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THEME ISSUE
GASTROENTEROLOGY AND HEPATOLOGY AT THE MOUNT SINAI HOSPITAL 1852–2000
Part I

Jeremy Hugh Baron and Henry D. Janowitz, guest editors

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Introduction

Jeremy Hugh Baron, D.M., F.R.C.P., F.R.C.S.,
and Henry D. Janowitz, M.D.

This publication began as two independent initiatives. After Dr. Janowitz became Chief of Gastroenterology at The Mount Sinai Hospital in 1958, he made inflammatory bowel diseases the main interest of the division. He had long intended to write the history of this topic after he retired as chief. Dr. Baron was a fellow in this division in 1961 – 1962, and after he retired (in 1996) from his national health and university service in London, he decided to devote his energies to the history of gastroenterology and to spend his winters in New York. Therefore, we joined forces to co-edit this history of gastroenterology and hepatology in time for the millennium in 2000 or the sesquicentenary of The Mount Sinai Hospital in 2002. We produced a list of topics, wrote some chapters, and invited colleagues to contribute their expertise. We express here our gratitude to all of them and to our secretaries, Sharon Nieman and Octavia Paul, for deciphering the illegible scripts; Janine Kail, for the medical records data; and Al Lyons, Richard Steele, and Barbara Niss, the Mount Sinai archivists, for their skilled assistance.

1

The Mount Sinai Hospital

A Brief History

JEREMY HUGH BARON, D.M., F.R.C.P., F.R.C.S.

Abstract

In 1852, The Jews Hospital was founded for the increasing number of Jews in New York. It opened in 1855 with 45 beds on West 28th Street; 92% of the patients were indigent. In 1864, the hospital formally became nonsectarian and, in 1866, changed its name to The Mount Sinai Hospital. The medical staff was primarily Jewish, because until relatively recently, it was difficult for Jewish doctors to obtain postgraduate training or specialist posts at major New York hospitals. As the Jewish population moved uptown, so did The Mount Sinai Hospital: in 1870 to 66th Street, and in 1904 to 100th Street, with 456 beds, growing with new buildings and services to the current 1100 beds, 50,000 discharges, 400,000 inpatient days and 300,000 outpatient visits each year.

Services increasingly became specialized, and then subspecialized. Key innovations included the choice of interns by competitive examination (1872), an advisory Medical Board (1872), the Nurse Training School (1881), the library (1883), the Alumni Association (1896), a professional medical hospital administrator (1903), research laboratories (1904), clinicopathological conferences (1905), the Social Services Department (1906), postgraduate teaching programs (1923), full-time chiefs of clinical services (1944), the dedication of the Mount Sinai School of Medicine (1968), and the merger in 1998 into the Mount Sinai-New York University Medical Center. **Key Words:** Mount Sinai Hospital New York, history

THIS CHAPTER HIGHLIGHTS some of the main events of the first hundred years of Mount Sinai (1–13). In the 1850s, the increasing population of New York City, frequently subject to overcrowding, poverty and disease, signaled the need for new hospitals to complement the older voluntary ones (New York Hospital, 1771; Lincoln, 1839; St. Vincent's, 1849) and the older municipal institutions (Bellevue, City). The increasing number of Jews in New York (16,000) led the Hebrew Benevolent Society in 1850 to plan a Jewish hospital. In 1852, they and the Young Men's Hebrew Association, the German Hebrew Benevolent Society, and the Assistance and Education Society formed Articles of Association (1). Land was bought on the south side of then-rural West 28th Street between 7th and 8th Avenues, ground was broken in 1853, and The Jews Hospital was opened May 17, 1855 with 45 beds (2). The hospital's services were intended primarily for the indigent, and of the 216 patients admitted in 1855–1856 only 16 could pay (3).

In the 1852 Articles of Association, the hospital was established for "medical and surgical aid to persons of the Jewish persuasion" (1) but from the beginning accident cases were admitted from all ethnic groups. In 1862, the Jews Hospital admitted soldiers from the Civil War. The following year, those injured during the Draft Riots were admitted (4). In 1864, a formal nonsectarian policy was adopted, but this policy was not widely recognized (5). To emphasize this change in policy, the hospital was renamed, in 1866, The Mount Sinai Hospital (5). Nevertheless, this change did little to diminish the anti-Semitism prevalent at the time.

In the 19th century and much of the 20th, Jews were not readily accepted into medical schools (14). Moreover, it was more difficult for them to obtain postgraduate training and even more difficult to become specialists at a univer-

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sity hospital. Some medical schools did not take any Jews, while some of the better schools, such as the College of Physicians and Surgeons ("P & S") Medical School at Columbia University, had a quota of only 10% Jewish students (14, 15). When Crohn qualified at P & S in 1906, he came to The Mount Sinai Hospital as an intern (16). When Janowitz qualified at P & S in 1939, second in his class, he was given a message that he should not expect an internship at Columbia, but should contact Dr. George Baehr at Mount Sinai, as should his friend (third in the class), whose "accent was too thick for the Harkness Pavilion" (16).

Some social exclusions were blatant. When Crohn attended to a patient vacationing in a hotel in Maine, he could not spend the night there, and when he went to an executive board meeting of the AGA in Pittsburgh, he found that he alone was lodged in a hotel because he could not stay with the other board members at the Fort Duquesne Club (17, 18). When Winkelstein went to meetings of the AGA in the 1920s, he could not stay in the main conference hotel (19). In 1962, I visited Dr. Morton Grossman's department in Los Angeles and one day was invited to have lunch with Stuart Tuttle at his country club. Dr. Grossman learned where I had visited and remarked that I had been entertained where Dr. Tuttle could never have taken him (20).

As the Jewish population of New York progressively moved uptown, The Mount Sinai Hospital followed. In 1870, it relocated to Lexington Avenue between 66th and 67th Streets (6), and then again in 1904 to Fifth Avenue at 100th Street (11). At the time of this second move, Mount Sinai had 456 beds. In 1855, the beds were divided into Medicine and Surgery. By 1875, when a separate outpatient dispensary was opened, gynecology and pediatrics cases were treated separately. From 1872, interns were chosen by a competitive examination and served two years (8). The Association of the Alumni of The Mount Sinai Hospital was created in 1896. The Mount Sinai Training School for Nurses was incorporated in 1881 (8). The medical library opened in 1883. The first medical adult sub-specialist, a dermatologist, was appointed in 1890, and a pathologist (Henry Heineman) and a neurologist (Bernard Sachs) in 1893 (10).

Sachs (21) enunciated the ethos of a Mount Sinai Hospital specialty service: "The chief aims . . . should be the considerate treatment of the patient, making use of the most recent methods, the training of an adequate House Staff, and, above all, the development of a group of able associates and assistants . . . who would be certain in the course of time to contribute materially to the advancement of neurological science. . . . Incidentally I stressed the importance of the doctor looking neat, being scrupulously clean, using good English, and articulating distinctly."

In 1903, Mount Sinai appointed Dr. S.S. Goldwater as the first professional medical hospital administrator in the U.S. (1). Dr. Goldwater maintained that health was not a privilege but a right, and he fought throughout his long career in New York to ensure that its citizens should be warm, well fed and sheltered. Under Dr. Goldwater's administration, The Mount Sinai Hospital's Social Service Department was opened in 1906.

The development of a medical school in The Mount Sinai Hospital took almost one hundred years. In 1873 the Board was asked, but considered it not expedient then, to start a medical school. In 1908, when the decision was made to take medical students from Bellevue and Columbia, the titles of clinical professor of medicine and clinical surgery were awarded to senior hospital staff. Clinical pathological conferences were held occasionally from 1905 and regularly from 1919. Formal postgraduate teaching programs began in 1923.

Research, too, flourished at Mount Sinai. When the Pathology Department was formally instituted in 1906, the 15 staff members were all engaged not only in routine clinical testing but in "active research work in . . . higher problems of modern medicine" (12). The philanthropist Adolph Lewisohn (a Mount Sinai Hospital trustee from 1898 to 1938) insisted that a first-rate hospital must be a first-rate research center; he therefore financed both with capital and revenue the laboratories built in 1904 and 1916. By 1923, there were 22 professional laboratory staff members. The laboratory directors became full-time salaried employees in 1926, Klemperer for morbid anatomy, Shwartzman for bacteriology and Heidelberger for chemical pathology. But there were also 60 volunteer researchers-clinicians who maintained an active clinical practice, seeing patients, but who also devoted more than 20 hours per work to research (22, 23). They were motivated by being associated with progress in scientific medicine, which was thought to lead to a higher level of clinical care. They also knew the Mount Sinai policy of promoting clinicians with a scientific background. Thus, over its first hundred years, The Mount Sinai Hospital evolved from a small community hospital into a major medical center which was recognized internationally for its excellence in clinical care, research and postgraduate teaching.

As an aside for the overseas reader, an explanation of the usual staffing structure of a major hospital may be helpful. In the 1850s all, and in the 1990s almost all, of the senior clinicians (consultants) were 'voluntary attending'; that is, they earned their livelihood in private specialist practice in their outside offices. They used the hospital only for the admission of patients to private beds. They were not paid for their hospital work in caring for patients in the wards, for operative procedures, or for research or undergraduate or postgraduate teaching. The post of attending was keenly sought, because even a voluntary staff position at a major hospital encourages other doctors to refer patients to the attending, or patients to refer themselves, and also because hospital privileges permit admissions of private patients whose care is facilitated by the "house staff" (interns, residents and fellows). Today there is also a large "full-time" salaried staff, but earlier this century only a few senior academic staff members, such as departmental or divisional chairmen, were salaried.

As early as 1872, the Hospital trustees were advised by a medical board. To avoid conflicts of interest or the diversion of funds to research activities, separate financing for research was instituted after 1925, with the encouragement of scientifically minded clinicians and pathologists. By 1937, joint committees were set up for research, administration, education, and the residency and fellowship program. In 1944, full-time chiefs of the clinical services were appointed, George Baehr directing the first medical service and medical research, followed by Isidore Snapper for the second service and graduate medical education. In the 1950s, the Board considered again the question of establishing a medical school, but these plans did not materialize until 1963, when the Mount Sinai School of Medicine of the City University of New York was incorporated. It now has about 400 medical students, 50 M.D./Ph.D. students and 130 Ph.D. students. The Mount Sinai Hospital now has more than 1100 beds, with approximately 50,000 discharges, 400,000 inpatient days, and 300,000 outpatient visits each year. In 1998, The Mount Sinai Hospital and New York University Medical Center agreed to merge into the Mount Sinai-New York University Health Services Organization, with NYU awarding degrees for two separate medical schools, the NYU School of Medicine and the Mount Sinai School of Medicine.

Thus, in a century and a half, The Mount Sinai Hospital grew from a tiny, 45-bed sectarian hospital serving an almost wholly indigent community into today's giant academic medical center, known for its clinical, scientific and teaching excellence.

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2

Gastroenterology and Hepatology as Subspecialties

Jeremy Hugh Baron, D.M., F.R.C.P., F.R.C.S.

Abstract

Gastroenterology grew as a subspecialty in Germany in the 19th century. In the 1880s and 1890s, Austrian and German clinics were attended by American physicians who, on returning to the U.S., founded the American Gastroenterological Association in 1897. The creation of a subspecialty board, however, had to wait until 1941. At The Mount Sinai Hospital, Dr. A.A. Berg was appointed Surgeon in 1899. His practice focused on the alimentary tract, which in 1910 became one of the four surgical specialties. In 1914, further subdivision led to the stomach and duodenum becoming additional specialties. In 1917, wards were endowed for Dr. Berg's specialty. The first Mount Sinai physician to have an interest in gastroenterology was Morris Manges, but the first to limit his practice to gastroenterology was Dr. Edward Aronson, for whom a specialist outpatient division was formed in 1913. Aronson died in 1922 and was succeeded by Dr. Burrill Crohn, who was followed in 1934 by Dr. Asher Winkelstein; all three collaborated closely with the surgeons, physiologists and biochemists. In 1958, Dr. Henry Janowitz became chief of the Division of Gastroenterology; he was succeeded in 1983 by Dr. David Sachar, who was followed in 1999 by his associate Dr. Steven Itzkowitz. In 1958 Dr. Fenton Schaffner became chief of the Division of Hepatology (now headed by Dr. Paul Berk), and in 1979 Dr. LeLeiko became chief of Pediatric Gastroenterology. **Key Words:** Gastroenterology, hepatology, history

Germany

The subspecialty of gastroenterology was created in Germany in the late 19th century, following the scientific advances in German clinics (1). To take the stomach as an example, Tiedemann and Gmelin measured the concentration of hydrochloric acid in 1824, the year after Prout's seminal presentation to the Royal Society, London. Muller and Schwann described pepsin in 1835, Enderlin found HCl in the stomach of a decapitated criminal in 1843, and Leube introduced the test meal in 1871 (1).

Ewald wrote the first textbook of gastroenterology in 1879, and his pupil Boas started the first gastroenterology clinic and laboratory, in Berlin, in 1886 (2). Boas called himself "specialist in gastrointestinal diseases" and in 1895 founded the first gastroenterological journal, *Archiv für Verdauungs-Krankheiten* (later *Gastroenterologia* and then *Digestion*). Meanwhile Ewald and Boas introduced the first fractional test meal in 1886, the year Jaworski and Gluzinski measured gastric secretion of HCl as the equivalent amount of a standardized concentration of NaOH/100 cc gastric juice used to titrate a 100 mL volume of gastric juice. In 1892, Ewald measured free and total acidity with Congo red and phenolphthalein indicators.

United States

The United States followed the German pattern (3, 4). In the 1880s and 1890s, many American physicians went to Austrian and German gastroenterological clinics and practiced this subspecialty when they returned. Moreover, many German gastroenterologists had emigrated to the United States. There were 17 founders of the American Gastroenterological Association in 1897. Einhorn was born in Poland. Hemmeter's

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parents were German and he was sent to school in Wiesbaden. Seven of the 17 learned their gastroenterology in Austria and/or Germany: Aaron, Eisner, Friedenwald, Hemmeter, Manges, and Stuckey visited Vienna; Friedenwald, Aaron, Einhorn, and Manges studied in Berlin; and Stuckey visited both Leipzig and Strasburg.

In Germany, academic physicians and clinicians, and even gastroenterologists like Leube and Ewald, opposed the efforts of Boas to detach digestive diseases from internal medicine. Unlike Einhorn and Pavlov, they refused to support Boas's journals, so that Boas was unable to convene a national conference on gastroenterology until 1914. There was similar opposition in the U.S., but the 17 physicians of 1897 did found the first national gastroenterological society in the world. A subspecialty board of gastroenterology came only in 1941. The American Gastroenterological Association formed its research group in 1956.

The first American textbooks on the stomach came in 1896 (Einhorn) and 1897 (Hemmeter). The first journal was *Transactions of the AGA* (1903–1908); *Digestive Diseases and Nutrition* appeared in 1934 and *Gastroenterology* in 1943 (1). Meanwhile, gastroenterological clinicians founded the Society for the Advancement of Gastroenterology (1932), which was renamed National Society for the Advancement of Gastroenterology in 1934, then the National Gastroenterological Association in 1938, and finally the American College of Gastroenterology in 1954 (5); its 1934 journal, *Review of Gastroenterology*, has been known as the *American Journal of Gastroenterology* since 1954.

Mount Sinai

Crohn was rarely reticent: "Without boasting, it is a fair statement to make that the profession of the country, or for that matter, the world over, look with expectation to the staff of this hospital when problems of a gastroenterological nature are up for discussion" (6). A clinically and scientifically organ-based specialty, to be successful, needs high-quality, multi-faculty components which work together. At The Mount Sinai Hospital, gastroenterology as a subspecialty actually began with Dr. A.A. Berg's appointment as surgeon in 1899 and his subsequent concentration on the alimentary tract. The first internal medicine physician to have an interest in gastroenterology was Morris Manges, one of the founders of the American Gastroenterology Association in 1897 (3). In 1910, surgery was formally divided into four specialties, one of which covered the abdomen; this specialty was further subdivided in 1914 into stomach and duodenum. In 1917, The Wimpheimer Wards for the Surgical Treatment of Diseases of the Stomach and Intestines were endowed for A.A. Berg. A separate proctology surgical clinic began in 1936 and was directed by Dr. Sylvan Mannheim.

In 1913, through Berg's influence on the medical board, a specialist outpatient division of medical gastroenterology was formed in Mount Sinai, to be headed by Edward A. Aronson, who was the first Sinai physician to limit his practice to gastroenterology. In this division, clinicians and laboratory staff worked on biochemical problems, especially variations in gastric and pancreatic secretion in health and disease, and in response to drugs.

Thus, at the time of the First World War, Aronson had a clinic but no beds, and Berg had beds on both adult and children's wards, biochemical support from Dr. Samuel Bookman, and physiological studies by Dr. Eugene Klein. Sunday morning grand rounds began at 9.30 A.M. when Berg's team (Richard Lewisohn, Paul Aschner, A.O. Wilensky, Eugene Klein) and Aronson's team (Burrill Crohn — "sometime conformist, often belligerent," Samuel Goldfarb "an amateur radiologist," Samuel Weiskopf, Eddie Hollander, S. Winfield Kohn, Asher Winkelstein) met in the Reception Ward (6, 7). There they saw special follow-up patients, especially those who had been given a gastroenterostomy for duodenal ulcer and cecostomy for ulcerative colitis. At 10:30 A.M., the teams moved to Berg's wards, M & N, where with the house staff, nurses and visitors they made rounds with open discussion until lunchtime.

Aronson died young in 1922 and was succeeded by his first assistant, Burrill Crohn, even though he was in bad grace with some of the senior staff for his unorthodox work and heretical criticism of gastroenterostomy (8, 9). In 1926, Crohn was given the title associate-in-medicine and the responsibility both of an attending and of clinical research. Crohn was succeeded by Asher Winkelstein in 1934. Their careers are outlined in chapters 3–5. When Dr. Ralph Colp became an attending in the 1930s, the multidisciplinary team continued. "Attached to the service was an internist, Dr. Samuel Averbuck; a psychiatrist; a gastroenterologist, Dr. Asher Winkelstein; and a gastrointestinal physiologist, Dr. Franklin Hollander. Ward grand rounds were formal, crowded with staff and visitors. After presentation of the case by the house surgeon, demonstration of the pertinent X-rays and the surgical specimen, the case was open for discussion, which included medical, psychiatric and physiological aspects. Later these were conducted off the ward at a formal conference" (10).

Henry D. Janowitz founded the first division of gastroenterology in the Department of Medicine in 1958 and headed it until 1983. Other associated divisions were created, such as Hepatology (Fenton Schaffner, 1958) and Pediatric Gastroenterology (Neal LeLeiko, 1979). Thus, gastroenterology became one of the new separate groups of internal medicine, each of which was headed by a physician ranked as an associate attending in medicine with responsibility for an outpatient clinic and, usually, a laboratory. Today The Dr. Henry D. Janowitz Division of Gastroenterology (named in 1992), headed by Dr. Steven Itzkowitz of the Department of Medicine, has a faculty of fifty. Dr. Paul Berk's Division of Liver Diseases has three, and Pediatric Gastroenterology has five attendings.

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3

Morris Manges and Edmund Aronson

JEREMY HUGH BARON, D.M., F.R.C.P., F.R.C.S.

Morris Manges (1865–1944)

MORRIS MANGES (Fig. 1) (1 – 3), the first trained gastroenterologist at The Mount Sinai Hospital, was born in New York City on May 10, 1865 and graduated Phi Beta Kappa from City College in 1884. He graduated in medicine from the College of Physicians and Surgeons, Columbia University in 1887. Manges then interned at the Charity Hospital on Blackwell Island (later renamed City Hospital on Welfare Island), including six weeks at the Maternity Hospital with Dr. Henry Garrigues, who had immigrated from Denmark in 1875 (4). Manges was greatly impressed by the total lack of deaths from puerperal sepsis in the four years before he had arrived. This was entirely due to Garrigues' application of the doctrines of Semmelweiss (isolation and antisepsis with careful cleanliness), which led in 1883 to the reduction of maternal mortality from puerperal sepsis from 25% to zero.

Manges spent 1888 and 1889 first with Ewald in the Königin Augusta Hospital in Berlin, and then in Frankfurt and Vienna. On his return to New York, he attracted a large practice, with patients coming from all over the U.S. because he had a sympathetic manner and good diagnostic skills, and because he spoke fluent German and had a wide knowledge of European medicine, so that he could recommend health resorts for his wealthier patients to attend (1).

In 1892, Manges became visiting physician to The Mount Sinai Hospital and was promoted to attending in 1898. At that time, he joined A. Merger, J. Rudisch and N.E. Brill. He also served as consultant physician to the Hospital for Joint Diseases and the Hebrew Orphan Asylum. In 1892 and 1896, he published his most lasting works, translations into English of Ewald's two-

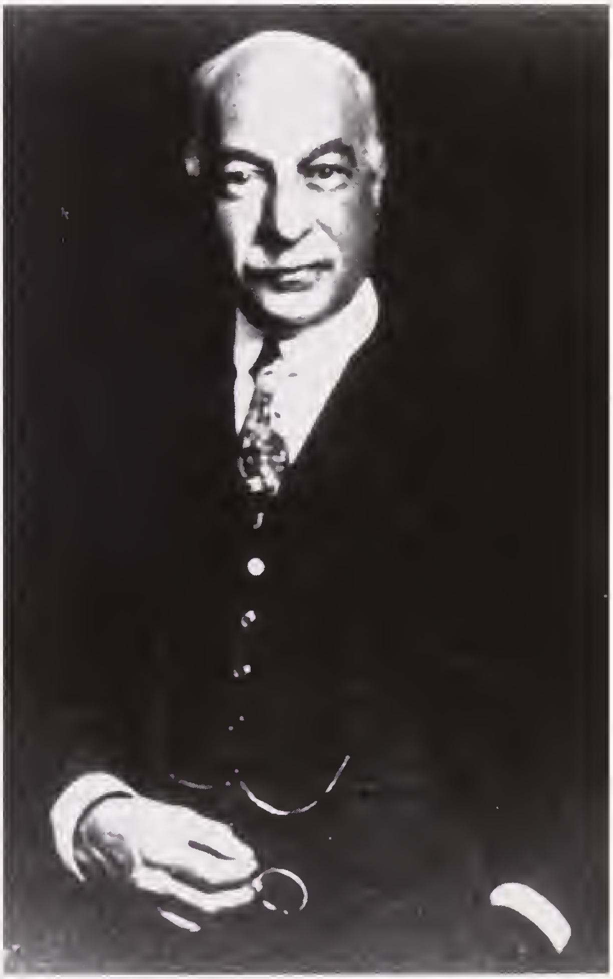

Fig. 1. Dr. Morris Manges.

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Key Words: Morris Manges, Edmund Aronson.

volume classic, *Diseases of the Stomach*. His other singular contribution to American medical history was to purchase from the Curies in 1902 the first specimen of radium for therapeutic use in the U.S.; he later presented it to the New York Academy of Medicine (5). He retired in 1921 but remained a consultant until his death on January 6, 1944.

Manges was a founding member of the American Gastro-enterological Association in 1897 and presented papers at its first two scientific meetings (Carcinoma of the cardia; A case of dilation of the stomach due to latent ulcer of the pylorus; and Operation by Halsted) as well as a detailed survey of stomach diseases at The Mount Sinai Hospital from 1898, at the seventh AGA meeting in 1904. Subsequently, he practiced and taught internal medicine. Crohn (6) commented: "He was really an internist and he contributed nothing to gastroenterology itself."

His non-gastroenterological publications, covering three decades (1890–1921) were protean in subject matter (7): a new rapid tubercle bacillus stain, quantitative estimation of sugar, mucous casts in the urine, treatment of typhoid fever, heart disease in the 18th century, therapeutics of heroin, treatment of coughs with heroin, secondary carcinosis in bone, rheumatism and gout, heart failure, pharyngeal diphtheria, exophthalmic goiter, pneumonia with pericarditis, ulcerative endocarditis, aneurysm, lysol in the treatment of meningitis, cholesterin pleurisy, rectal hypnotics, treatment of pneumonia, meningitis, adherent pericardium, aortic stenosis, abuse of water drinking, liberal diet in typhoid, typhoid fever in the aged, perforation in typhoid, the physician and the medical press, tuberculous pericarditis, lateral thoracic glands, prolonged fevers, whispered bronchial voice, heart disease and epigastric symptoms, mouth, diabetes, eventration of the diaphragm, early diagnosis of cancer, lung abscess, non-tuberculous pulmonary suppuration, pulmonary endarteritis, pulsating spleen, roentgen ray diagnosis, and periarteritis nodosa.

Outdoor recreation and the environment were important to him. He loved the arts, painting in watercolors outdoors, exhibiting at the American Physicians' Art Association, and collecting engravings, etchings and French bronzes. He had a fine scientific and archaeological library, and he was a member of the Archaeological Institute of America and the Oriental Institute of the University of Chicago.

Manges was an excellent lecturer, and from 1898 to 1908 he was professor of clinical medicine at the New York Polyclinic Medical School. From 1911 to 1922, he taught at New York University and Bellevue Medical College. He strongly supported the role of science and research at Mount Sinai, then a non-university hospital. In the 1890s, he was also compassionate enough to break the City Board of Health's rigid quarantine rules by smuggling a child with scarlet fever out of a well-known New York hotel into a building at The Mount Sinai Hospital used to quarantine patients. He ensured total secrecy of the doctors, nurses and attendants, which led to the child's grateful and wealthy mother buying land on East 16th Street to establish the Minturn (later Willard Parker) Isolation Hospital in 1896 (8).

For his era, Manges was unusual in his modesty; when he cited Ewald's book, it was in the format "see Ewald's *Diseases of the Stomach*, American translation, p. 47," thereby concealing his own role as translator (9).

Edward Aaron Aronson (1874–1922)

Edward Aronson (Fig. 2) was born in New York and qualified at Columbia University in 1899 (10). He followed the custom of seeking postgraduate training in Germany; like Manges, he worked with Ewald at the Königin Augusta

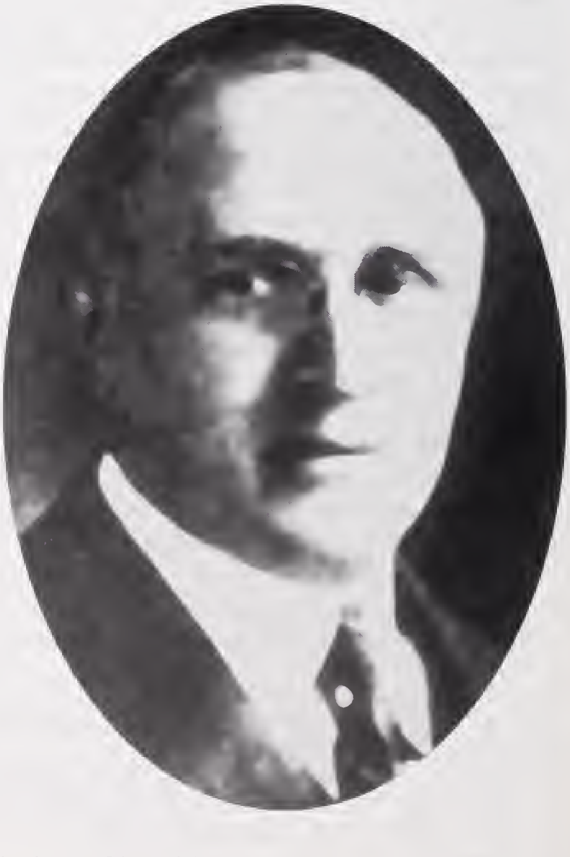

Fig. 2. Dr. Edmund Aronson.

Hospital in Berlin (11) and also with Theodor Rosenheim for esophagoscopy (12).

On returning to New York, he served as instructor in the Medical Schools of Fordham University and the College of Physicians and Surgeons, as well as the New York Polyclinic. He came to Mount Sinai to join Dr. Bookman in the physiological chemistry department of the pathological laboratory, and investigated the chemical composition of the urine in such diseases as typhoid, pernicious anemia and tetanus (13).

Presumably as a result of his scientific training, he was appointed in 1913 as Mount Sinai's first chief of gastroenterology. In his 11 years as chief, he built a small team of clinical investigators and began that close cooperation with the gastrointestinal surgeons which has been such a strong feature of hepatogastroenterology at The Mount Sinai Hospital during this century (see chapter 2). However, he appears to have done little or no research, and his few papers are mostly clinical case reports or reviews. He died on June 24, 1922, at the age of 47, during an operation for pancreatitis.

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4

Burrill B. Crohn (1884–1983)

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Burrill B. Crohn (1884–1983)

BURRILL B. CROHN (Fig.) was not the first or only Mount Sinai Hospital physician to have a disease named after him. But "Crohn's disease" continues to resonate worldwide and probably will continue to do so even after the etiology of this enigmatic illness is discovered.

Burrill Crohn was one of twelve children born into a German-Jewish immigrant family. His father settled in New York City and earned a livelihood as a stockbroker. The children never lacked the necessities of life, but had to forego its luxuries. At age 13 (1907), Burrill entered the City University of New York; he graduated at age 18. He obtained his medical degree from Columbia University's College of Physicians and Surgeons after four years. Having passed a comprehensive examination, he was appointed to The Mount Sinai Hospital for a two-year rotating internship and a year's fellowship in a clinical laboratory under the direction of Emmanuel Libman (of Libman-Sachs endocarditis). This was the conventional pathway of bright young men at that time at The Mount Sinai Hospital.

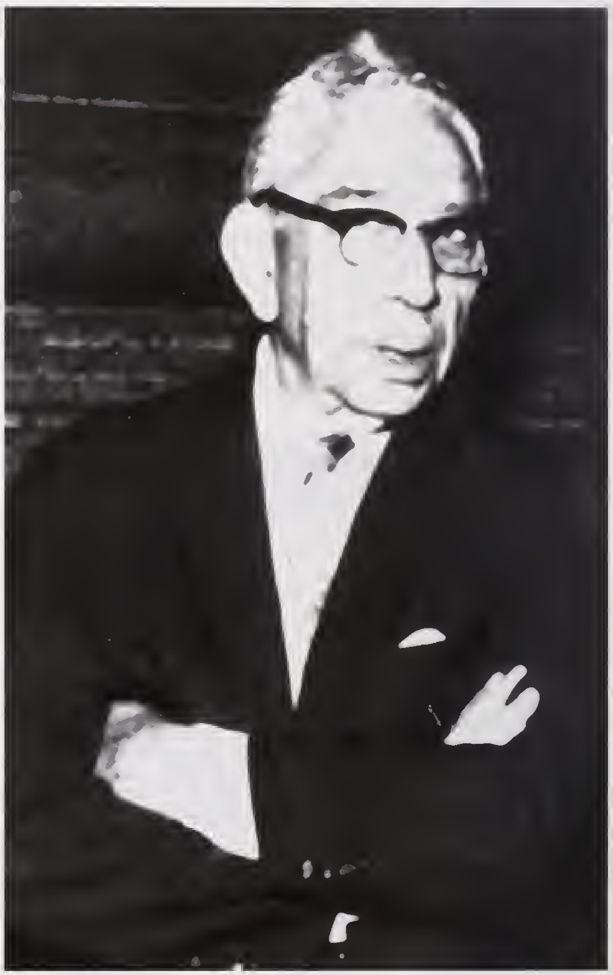

Fig. Dr. Burrill B. Crohn.

In later years, Crohn wrote a short personal biography entitled *Notes on the Evolution of a Medical Specialist 1907–1963* (1). It is delightfully written and gives a picture of his development as he saw it. I had met him, of course, when I entered Mount Sinai for my own internship just seven years after the publication in the *Journal of the American Medical Association* of the paper on regional enteritis, and was amused by the slightly skeptical medical atmosphere which surrounded the importance of this curious entity of 14 cases. (Hugh Baron's account of the discovery of this disease in chapter 19 [Mt Sinai J Med 2000; 67(3): in press] is, in my opinion, the most even-handed and detailed account of the road that led to its discovery.) When I returned to

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Key Words: Burril B. Crohn.

Mount Sinai in 1948, after World War II, I got to know him more closely. Indeed, when I needed office space to moonlight during the eight years I spent in Frank Hollander's laboratory, Burrill graciously allowed me his office in the evenings and on weekends. For a period of six months, I helped him in the morning sessions when he saw his patients. It became clear that his persistent and scholarly recording and substantive writing about regional enteritis had convinced his institution that his subject was going to be an important one.

Even Nobel Laureates make only one important observation. It should be noted that Crohn had already established himself as a clinical investigator in his early work on "Affections of the Stomach" (2) long before his ileitis studies. Burrill had contributed to the joint venture with the observations of Leon Ginzburg and Gordon Oppenheimer. I recall the efforts that Dr. Richard Marshak, his radiologist, made to convince Burrill that regional enteritis could also occur in the colon, but without success. Burrill eventually accepted this concept after it had been accepted by the entire world.

In 1935, he was elected president of the American Gastroenterological Association. During the brief period of my daily contact with him, he enjoyed a great clinical practice and was becomingly modest about his role in the discovery of regional enteritis. In my presence, he never used the term "Crohn's disease" which he ascribed to the writings of the English surgeon Brooke (3). He was a good general practitioner of gastroenterology, not a master of internal medicine, but his intuitive grasp of a patient's psychology made him outstanding in the handling of functional disorders of the GI tract. His approach to Crohn's disease was firmly based on detailed records of his experience, and he was an ardent exponent of steroids for Crohn's disease as well as ulcerative colitis. He thought these disorders were infections, probably of viral origin, and saw no reason why a patient might not have both diseases, although he considered this rather rare.

He enjoyed taking care of the famous, but was compassionate and supportive of his poor patients. He looked for a son in the young men who worked for him and had difficulty in realizing why they could not accept this role. He was educated, cultured and a well-read physician. His second marriage, to Rose, was a happy and fulfilling one. After his death, his family founded the Burrill B. Crohn Research Foundation to support the research in the disease at The Mount Sinai Hospital. Shortly before her death, Mrs. Crohn endowed the Burrill B. Crohn Chair in Gastroenterology for the head of the service. David Sachar was named to be the first in the line of future holders of the chair. Mrs. Ruth Dickler, his daughter, continues to play an important part in the work of the Crohn's Foundation and his son, Sylvan (Woody) Crohn, practices medicine in upstate New York. I was particularly happy that Burrill, along with Leon Ginzburg and Gordon Oppenheimer, accepted the role of honorary chairman of the National Foundation for Ileitis, Crohn's and Colitis (NFIC) of America (now known as the CCFA) (see Mt Sinai J Med 2000; 67(3): in press).

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5

Asher Winkelstein (1893–1972)

Henry D. Janowitz, M.D.

Asher Winkelstein (1893–1972)

Asher Winkelstein (Fig.) was born in Syracuse into a music-loving, prosperous, middle class business family and spent his medical career at The Mount Sinai Hospital in a transitional period (1920 – 1950) just before the renaissance of modern gastroenterology. Educated at Syracuse University and the college of the medical school there, he served a two-year rotating internship at Mount Sinai and spent a year in a clinical laboratory, essentially a clinical pathology laboratory, under the volunteer direction of Dr. Emmanuel Libman. Dr. Winkelstein went into private practice after a preparatory period of 3¹/2 years.

I first met him in 1939, when I arrived at Mount Sinai for my internship, and got to know him more closely after returning to Mount Sinai after World War II in 1950. Dr. Winkelstein's scientific training may have been fragmentary, but his curiosity was endless and he was intelligent, active and gifted. These qualities enabled him to make numerous significant clinical observations in gastroenterology. I never found out what directed him to gastroenterology, but I am sure two outstanding chiefs of surgery, Ralph Colp and John Garlock, who were interested in surgery for the treatment of peptic ulcer and diseases of the esophagus respectively, were major influences in his choice of a nonsurgical gastroenterology course.

It is necessary to realize the low status of gastroenterology in those years and understand that it took a considerable amount of courage to enter the field. The chief of medicine during my years at Columbia University's College of Physician and Surgeons (1935 – 1939) made clear his disdain for the field. Furthermore, from its founding, The Mount Sinai Hospital had never had an independent GI service, only a GI clinic, until the establishment of the current division in 1958 by Dr. Alexander B. Gutman, the first full-time head of medicine. Such distinguished clinicians and gastroenterologists as Burrill B. Crohn and Asher Winkelstein never made active medical ward rounds in the hospital, but served as chiefs of the

Fig. Dr. Asher Winkelstein.

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Key Words: Asher Winkelstein.

GI clinic. Winkelstein, succeeding Crohn, was my own clinical chief during the years 1950–1958.

In his oral history, recorded by Dr. Albert Lyons, archivist of the hospital, in October 1965, following his retirement in 1958, Asher Winkelstein rated his most important findings in this order. The first was the invention of the milk drip therapy for ulcer and peptic esophagitis (chapter 4). The second was the description of peptic esophagitis, reported in 1934 at the Cleveland Meeting of the AMA in a paper entitled "Peptic Esophagitis: A New Clinical Evidence" (chapter 8). The third was his role, along with the young, soon-to-die Eugene Klein, in persuading Dr. Ralph Colp to perform anterior vagotomy along with gastroenterostomy for peptic ulcer disease (this occurred long before Dragdstedt had published his paper on bilateral vagotomy [chapter 10]). Finally, his studies of nocturnal acid secretion in peptic ulcer disease were a considerable advance (chapter 9). I would rate the description of peptic esophagitis as the most important of this group and outstanding in itself.

Dr. Winkelstein died in 1972. I am certain that, had he been alive today, Asher would have easily accepted the *Helicobacter pylori* theory of gastric and duodenal ulcer and gastritis. He greeted with enthusiasm the new advances that were just being made. He suffered from not having a laboratory under his control, and he proposed more experiments in an afternoon than a team of workers could accomplish in a lifetime, but he was never discouraged for long. Music was a great solace to him; Asher had been a talented amateur violinist and supported himself during college as head of a musical group.

According to his son, Asher felt his professional career had been a successful and a happy one, climaxed by his appointment as clinical professor of medicine and gastroenterology when the new medical school was founded at Mount Sinai. He was survived by his wife, Celia, for six years until she died at the age of 75, and also by his children, Charles, a Mount Sinai professor of psychiatry, and his daughter, Clara, an academic professor of education teaching at Roosevelt College in Chicago.

6

Franklin Hollander (1899–1966)

JEREMY HUGH BARON, D.M., F.R.C.P., F.R.C.S.,
AND HENRY D. JANOWITZ, M.D.

FRANKLIN HOLLANDER (Fig.) was born in New York on January 19, 1899 and educated there (1–3). While studying for his B.S. in mathematics and chemistry at Columbia (1919), he worked as an assistant and instructor in chemistry (1917–1923); he received his Ph.D. in physical organic chemistry in 1924 after a year as a research chemist in the petroleum industry. After spending a further year as a consultant in chemistry, he began a 40-year career in physiology and physiological chemistry. Hollander became a medical fellow of the National Research Council with Lafayette Mendel at Yale from 1925–1927, studying gastric secretion. He then did a five-year stint as assistant professor in physiology at New York Medical College, taking his pouch dogs every summer to the biology laboratory of Cold Spring Harbor, Long Island.

From 1934–1936, Hollander was research associate and secretary of the Columbia University Dental Caries Research Group. With his mathematical skills and the statisticians of the Metropolitan Life Insurance Company, he studied the incidence of dental caries in a control population of more than 12,000 persons and in a group presenting for dental treatment. He found that the total number of decayed tooth surfaces per person was a more sensitive index of the extent of dental disease than the number of decayed teeth per person (4).

Hollander's final 30 years were spent at Mount Sinai, as chief of the gastrointestinal physiology research laboratory. During these years, he had many outside scientific commitments, as lecturer (later assistant clinical professor) at Columbia and as research adviser on chemical warfare (1943–1944), working on the therapeutic use of aerosols in gas casualties.

Fig. Dr. Franklin Hollander.

From 1954–1959, he was consultant in gastric physiology to the cancer center division of the New York City Department of Health, and from 1960, a member of the NIH Research Grants general medicine study section. He was associate editor of the *American Journal of Digestive Diseases and Nutrition* from 1940–1943, when

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Key Words: Franklin Hollanderr.

he took a similar position with the new journal, *Gastroenterology*, becoming its abstract editor in 1953. From 1961, he was on the editorial board of the *Journal of Applied Physiology* and the *American Journal of Physiology*, and from 1963, the section editor for the latter for gastrointestinal physiology.

Hollander saw his role at The Mount Sinai Hospital as many faceted (5), but his first priority was research into physiological problems of immediate clinical importance in the hospital. His laboratory, in conjunction with the clinical staff, helped evaluate the efficacy of the intragastric drip for peptic ulcer, a new statistical procedure for assessing the results of ulcer surgery, a new bioassay for male sex hormone in urine, a study on the effect of artificial fever on gastric secretion, his insulin test for vagus nerve continuity, and a synthetic diet for jejunal feeding. His second aim was to pursue basic long-range physiological problems, in light of John Dewey's maxim that "it does not pay to tether one's thoughts to the post of usefulness with too short a rope." With this purpose in mind, Hollander studied the mechanism by which hydrochloric acid is produced in the stomach, and the role of mucus in gastritis, peptic ulcer, stomach cancer, and human sterility. His third role was in postgraduate education, teaching classes in normal and pathological physiology, and in statistical methods, as well as taking part in the various conferences, grand rounds and seminars. Fourthly, he gave both general and specific advice to other departments in the construction of their own formal research projects.

Despite his many activities, Hollander always considered his role as director of the gastrointestinal physiology laboratory as his principal one. Recruited by Drs. Ralph Colp and John Garlock, each director of a surgical service, Hollander arrived at Mount Sinai at a time when gastroenterology was a branch of surgery. Thus, he was a Ph.D. in a sea of M.D.'s. By his influence, gastroenterology at The Mount Sinai Hospital took its place as a scientific discipline. Although unable to deal with patients in the hospital directly, he soon attracted a group of young, eager and talented physicians and surgeons with whom he carried on a fruitful collaboration and in whom he took pride. These included Albert Cornell, Asher Winklestein, Vernon Weinstein, Henry Janowitz, David Dreiling, and Lawrence Werther.

Of his own achievements, it is clear from his writings and private comments that he valued most his description of the composition of the two components of gastric juice (the parietal and the nonparietal; see chapter 9), and the two components of the gastric mucosal barrier (see chapter 11).

Hollander was a strict and firm mentor who demanded clear hypotheses and supporting statistics before allowing a new research project to go forward. His wit was a dry one, but his personal support was generous. For thirty or more years, his tact in managing the conflicting demands of administrators, physicians, surgeons, and would-be scientists allowed him to maintain the integrity of his research laboratory, which could not continue without him after his untimely death from cancer of the pancreas.

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7

Gastroenterology and Hepatology

The Diagnostic Data

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Abstract

The Annual Reports of the Mount Sinai Hospital from the 1850s, and the *Mount Sinai Hospital Reports* for 1897 – 1906, make it possible to trace the discharges of gastroenterological inpatients, and (for a few years) of outpatients. Fully computerized diagnostic data have only been available since 1986. In the 19th century, about 20% of the outpatients had digestive disorders, the commonest of which were gastralgia/gastritis/dyspepsia, gastroenteritis, oropharyngeal complaints and constipation. A similar proportion of inpatients had digestive diagnoses, but the four disorders listed above decreased markedly in the second half of the 19th century, so that by the turn of the century the commonest diseases were typhlitis (appendicitis), hemorrhoids and other anal problems. By the 1990s, digestive diseases accounted for only 5% of total admissions, hepatobiliary diagnoses being the commonest group. Some cancers such as gastric and esophageal showed little change, while colorectal increased markedly. Some newly recognized diseases, such as peptic ulcer, waxed and then waned, while colitis and regional enteritis came and have continued to increase. Other new diagnoses, such as autointoxication and visceroptosis, flashed into prominence and then disappeared totally, presumably because they were nondiseases. **Key Words:** Gastroenterology, hepatology, diagnostic data.

This chapter discusses the numbers and diagnoses of patients with digestive and liver diseases in The Mount Sinai Hospital from its founding. In this hospital, as in other medical centers, patients were treated by internists and general surgeons until the subspecialties were recognized. For example, the first patient to be admitted to Mount Sinai, on June 5, 1855, was operated for (and cured of) fistula-in-ano (1, 2), and the first paper in Volume 1 of the bound *Miscellaneous Writings by the Attending Staff of Mount Sinai* is on gastrotomy for esophageal stricture (3).

Many of the great hospitals in the 19th century published detailed annual reports. Fortunately, it is possible to extract from most of the *Annual Reports of Mount Sinai Hospital* from 1855 complete lists of the diseases of inpatients and in some years also of outpatients. These lists were at first in Latin, but English terms soon appeared, and all the diseases were in English by the 1870s. Fatalities were usually noted and there were separate listings for surgery, and for children from 1877. Surgery was divided into 1st and 2nd divisions in 1900, as was medicine, in 1906. The short-lived *Mount Sinai Hospital Reports* (1897 – 1906) give remarkably full details of the gastrointestinal conditions of the inpatients of the medical, pediatric and surgical services during these ten years, classified by sex and outcome (cured, improved, unimproved, died). Such detailed data did not become available again until 1986, when the records were fully computerized by diagnosis.

The data extracted from the reports from 1855 – 1995 have been collated to provide total admissions and deaths at Mount Sinai, together with the total number of hepatogastroenterological diagnoses and fatalities irrespective of department, and the proportion of total admissions in these years, so that trends in incidence and fatality of the various diseases over the 140 years can become apparent. For simplicity, the data from both sexes have been combined.

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Clearly, there have been problems in disassembling the original data and then reassembling the figures into useful tables. Patients were often transferred between departments in one admission and may have been counted twice. Some patients may have had more than one diagnosis, so the sum of diagnoses may be greater than the number of admissions. Moreover, the changing pattern of diseases and the changing nomenclature required certain clarifying decisions.

In the 19th century, alcoholism and oropharyngeal diseases were classified as digestive diseases and have therefore been included in all tables. Alcoholism includes delirium tremens, inebriation and intoxication. Diseases of the oropharynx include dental caries, odontalgia and periodontal disease; mouth abscesses, gingivitis, palatal ulcers, pyorrhea, stomatitis; croup, pharyngitis and tonsillitis/amygdalitis (acute, follicular, hypertrophic, suppurative). Gastric and gastroduodenal catarrh, dyspepsia, gastrorrhagia and indigestion are included in gastralgia, which is a neutral word I have chosen to indicate any upper abdominal discomfort, now often called non-ulcer dyspepsia. In 1902, Brill (4) concluded that "an attack of gastralgia terminates with the eructations of gas and the pain is usually relieved by pressure in the epigastrium. [However,] there can be little doubt that many of the so-called cases of gastralgia or stomach cramp are really attacks of gall-stone colic." Lilienthal, in 1911, found that 55% of 82 of his private patients with gall bladder disease, and an even higher proportion of the 100 ward cases a year at Mount Sinai, had been previously diagnosed as having stomach trouble (5). Gastritis has been classified as in the original reports, but in the absence of endoscopy, histology and radiology, all these patients should be considered as having gastralgia, although some must have had peptic ulcers. The diagnosis "stomach (functional)" includes gastric neurosis, neurasthenia, hysteria, and hyperchlorhydria nervosa. Infective hepatitis includes catarrhal jaundice. Constipation includes fecal impaction and obstipation. Enteralgia was defined in 1879 by Wardell (6) as a painful affection of the intestines of neuralgic character, generally accompanied with constipation and flatus. Enteritis includes diarrhea, enterocolitis, dysentery, gastroenteritis and (gastro)intestinal catarrh. Abdominal pain, colic, enteralgia, functional pain, gas, mucous and neurasthenic colitis are included in "irritable gut," a neutral phrase chosen to indicate any lower abdominal discomfort, with or without bowel disturbances. Included in this diagnosis is the ancient term "intestinal colic," defined by Begbie in 1879 (7) as "severe pain in the abdomen (in a restricted view, in the colon), occurring in paroxysms, not stationary, but on the contrary moving from place to place, accompanied by a sense of constriction and tearing, for the most part also by that of expulsion." In 1902, Brill categorized this colic: ". . . the pain is usually centered about the umbilicus, is not as agonizing as in gall-stone colic and is relieved by the passage of flatus and by firm pressure" (4). Ulcerative (entero)colitis includes acute, catarrhal, chronic, croupous, membranous, necrotic, subacute and ulcerative colitis. Appendicitis includes cecitis, typhlitis and perityphlitis. The term "autointoxication" was used at Mount Sinai only between 1898 and 1906 and does not correspond to any modern diagnosis. In 1905, Brill (8) defined it as "an infectious disease of definite clinical aspects . . . having somewhat the picture of typhoid fever. . . ." and cited Cumston's 1898 paper, "Autotoxaemia" (9, 10). Although that paper refers to toxins produced by most organs in the body, including the stomach and intestine, with little or no resemblance to the Mount Sinai term, Koplik (11) embraced the concept of gastrointestinal autointoxication when he attributed transitory attacks of renal failure to episodes of alternating constipation and mucus diarrhea (mucous colitis) in which intestinal toxins are absorbed. Hemorrhoids and anal diseases have been included, but other purely surgical conditions have been excluded. Visceroptosis includes enteroptosis, gastroptosis, and hepatoptosis.

Clinical Data

Any history of a clinical speciality must first try to identify the patients' complaints and the doctors' diagnoses during a particular decade. Today there are national surveys of samples of whole populations, of visits to primary care physicians and clinics, and hospital admissions. The data presented here are of digestive disorders extracted from the *Annual Reports of The Mount Sinai Hospital.*

Deaths in New York

In 1852, there were 21,601 reported deaths in the city of New York (Manhattan), of which only 3137 were in hospitals or public institutions, and 5281 were deaths of infants under the age of one year. The city's population was then 558,412. The commonest cause of death, numbering 3397, was from some diarrheal illness, of which 1774 were certified either as diarrhea, dysentery or inflammation of the bowel, 1527 as cholera, and 96 as typhoid. The other conditions killing more than 500 were consumption (2487), convulsions (1680), stillbirths (1405), inflammation of the lungs (1062), marasmus (971), dropsy of the heart (882), typhus (662), apoplexy (653), scarlet fever (613), and croup (595).

Outpatients

For the general population served by the hospital, the least biased data are those of the outpatients seen in the Dispensary, where any sick person, however poor and irrespective of ethnic origin, would be seen and if necessary given medication. There are detailed diagnoses for two periods, the nine years of 1860 and 1864–1871, between which total attendance increased from 90 to 981 and gastroenterological attendance increased from 20 to 159. For the three years 1877–1879, total attendance averaged 10,159 annually, of which 2156 were gastroenterologic (Table 1).

Thus, the proportion of outpatients with gastroenterological problems increased by one-third from 15% to 20%, between the 1860s and 1870s. Their ten commonest complaints, expressed as proportions of total attendances or of gastroenterological diagnoses, are shown in Table 2.

The commonest GI complaint of outpatients in the 1860s as in the 1990s was upper abdominal pain (40%), which was only slightly less common (31%) in the late 1870s. Enterohepatological infections, probably mostly bacterial but some certainly due to worms or viral hepatitis, increased from 28% to 41% in this period, probably from overcrowding with poor sanitation, contaminated water and food. Constipation and hemorrhoids were together about as frequent as oropharyngeal disease (13%), mostly pharyngitis and tonsillitis (probably bacterial); all are rarer today with less overcrowding and the availability of antibiotics. In the 1990s, one of the commonest diagnoses by a gastroenterologist is some form of irritable gut, which was probably underdiagnosed in the 1860s (5%) and 1870s (2%).

TABLE 1

Outpatients. 1860-1871, 1877-1879.

Year	1860	1864	1865	1866	1867	1868	1869	1870	1871	Annual Mean 1860-1871	1877	1878	1879	Annual Mean 1877-1879
Total	90	310	437	459	619	743	906	1064	981	623	10,996	9,858	10,727	10,519
GI	20	54	71	67	113	88	122	170	160	96	2,308	2,227	1,923	2,156
GI%	22	17	16	15	18	12	13	16	16		21	23	18	20
Alcohol			2					2		–	4	19	8	
Oropharynx	5	7	2	0	13	11	20	35	19	12	380	203	245	275
Esophagus — misc.											3	3	2	
(Gastro)enteritis		12	22	20	26	27	31	29	50	24	795	778	541	705
Internal Obstruction											3	8		4
Peritonitis				2		1	2	1		1				
Peritoneal Malignancy								1		–				
Liver Abscess													2	1
Cirrhosis											22	22	44	29
Enlarged		2						1		–		1		–
Misc.		1								–		2	1	1
Catarrhal Jaundice		2	2	2	1		1	1	6	2	39	32	28	33
Gallstones												2		1
Parasites — Ascaris	1									–	181	112	70	121
Taenia		1		1		2			1	1	17	16	39	24
Stomach Cancer											3	5		3
Gastralgia	8	19	31	34	49	22	39	80	62	38	672	729	570	657
Gastric Ulcer											6	14	21	14
Colon Carcinoma							1	1	2	–				
Constipation	5	7	9	6	11	11	6	5		7	34	175	191	133
Colitis											17	34	5	19
Irritable Gut					8	8	8	7	10	5	6	40	70	39
Typhlitis	1			1			3			1	2	3	3	3
Hemorrhoids		2	3		5	6	9	5	9	4	101	32	34	56
Anal		1		1			2	2	1	1	23	19	37	26

TABLE 2

Outpatients (OPD). Ten Most Common Diagnostic Groups.

	1860, 1864-71		1877-1879	
	% total OPD	% GI OPD	% total OPD	% GI OPD
1. Gastralgia	6.1	40	6.2	31
2. Gastroenteritis	3.8	25	6.7	33
3. Oropharynx	1.9	13	2.6	13
4. Constipation	1.1	7	1.3	6
5. Irritable Gut	0.7	5	0.4	2
6. Hemorrhoids	0.7	5	0.5	3
7. Infective Hepatitis	0.2	2	0.3	2
8. Worms	0.1	<1	1.4	7
9. Cirrhosis	0	0	0.3	1
10. Anal	0	0	0.2	1
HGI infections 2 + 7 + 8	4.2%	28%	8.3%	41%

TABLE 3

Annual Admissions and Deaths (in Parentheses) for Total Cases and for Digestive Diseases.

Decade	1855-1865	1866-1876	1877-1886	1887-1896	1897-1906	1986-1995	1996*
Total Admissions/year	397 (35)	825 (55)	1709 (141)	2635 (236)	3541 (396)	41,841 (1246)	47,929 (1264)
Fatality %	9%	7%	8%	9%	11%	3%	3%
1. Alcohol excess	3	3 (1)	2	1	0	14	1092 (31)
2. Oropharynx	7	13	28 (1)	15	1	3	246 (13)
3. Esophagus Cancer		<1	1	1	8 (3)	8 (2)	54 (8)
4. Esophagus — misc.†		1	1	1	5	130 (4)	1443 (114)
5. Gastric Cancer	<1	1	3 (2)	6 (2)	23 (8)	13 (3)	178 (20)
6. Gastric — misc.†	25	28	50	85	44 (2)	89 (1)	797 (40)
7. Gastric / Peptic Ulcer†		<1	4	3	10 (1)	73 (3)	490 (22)
8. Duodenal / Jejunal Ulcer†					1	72 (4)	254 (27)
9. Hematemesis — ?site		<1	<1			120 (10)	446 (70)
10. Pancreas Cancer			<1		2 (1)	20 (5)	479 (34)
11. Pancreas — misc.†					3 (1)	87 (3)	420 (29)
12. Liver Cancer 1°		1	3 (2)	3 (2)	7 (4)	18 (6)	292 (33)
2°						16 (8)	753 (76)
13. Liver — Cirrhosis†		1	4	5 (1)	8 (2)	155 (28)	878 (211)
14. Liver — misc.†	2	6 (1)	10 (1)	12 (4)	16 (7)	159 (28)	1823 (328)
15. Biliary†		<1	3	8 (1)	59 (10)	107 (4)	1278 (51)
16. Gastroenteritis†	11 (1)	17 (1)	52 (7)	29 (6)	33 (8)	29	1537 (99)
17. Enteritis, e-colitis†						220	544 (6)
18. Int. Obstruction		<1	<1	4 (2)	11 (6)	65 (2)	1081 (60)
19. Worms		<1		1	1	1	4
20. Peritonitis†	2 (1)	3 (2)	8 (5)	10 (4)	7 (3)	15 (2)	291 (20)
21. Colorectal Cancer		1	4 (1)	6 (2)	14 (6)	50 (4)	509 (19)
22. Irritable Gut	<1	1	1	3	5	8	144
23. Colitis		1	2	17 (2)	17 (2)	193 (1)	320 (3)
24. Constipation	<1	1	4	21	17	13	239 (9)
25. Hemorrhoids	2	7	17	81	55	7	105 (3)
26. Anal	2	4	22	63	73 (1)	25	226 (4)
27. Appendicitis	<1	2	5 (1)	42 (9)	221 (27)	8	234
28. Diverticulitis						140 (4)	428 (11)
29. Visceroptosis					2		
30. Autointoxication					19		
31. Abdomen — misc.						6 (2)	
32. Colon — misc.†						28	370 (17)
Total GI admissions	55 (2)	95 (5)	226 (20)	418 (35)	676 (92)	1902 (124)	16, 955 (1358)
GI Deaths %	4%	5%	9%	8%	14%	6%	
GI Adm. as % Total	14%	12%	3%	16%	19%	5%	
Fatality Ratio	0.4	0.7	1.1	0.9	1.3	2.3	

The number of deaths is shown in parentheses.
* The 1996 GI figures are for diagnoses, not for individual patients.
† Diagnoses so marked are further analyzed in the following Notes.

TABLE 3

Notes for GI Diagnoses 1996.

4. **Esophagus — misc.**, 1443 (114),
   diaphragmatic hernia 297 (6), esophagitis 97 (9), reflux 408 (15), stricture 61 (7), ulcer 64 (9); achalasia 27, diverticulum 20 (1), dyskinesia 26 (1), dysphagia 230 (20), foreign body 6, hemorrhage 15 (4), perforation 3, varices 193 (41); other 16 (1).

6. **Gastric — misc.**, 797 (40),
   angiodysplasia, 27 (1), anorexia nervosa 3, bulimia 6, eating disorder 3, benign tumor 17 (1), dilation 4 (1), functional 33; Gastritis 60 (8), acute 35 (2), alcoholic 8, atrophic 60 (3), gastroduodenitis 148(3), + hemorrhage 124(8). Mallory-Weiss 39 (9), nausea/vomiting 174, pyloric spasm/stenosis 56 (4).

7. **Gastric/Peptic Ulcer,** 490 (22),
   gastric ulcer 67 (4), + hemorrhage 101 (7), + obstruction 3 (1), + perforation 4 (1); peptic ulcer 300 (6), + hemorrhage 14(3), + perforation 1.

8. **Duodenal /Jejunal Ulcer and other Duodenal Diseases,** 254 (27),
   duodenal ulcer 68 (4), + hemorrhage 104 (15), + obstruction 2, + perforation 7; jejunal/marginal ulcer 12 (1). There were additional patients with duodenitis 45 (3), and other 16 (4).

11. **Pancreas — misc.**, 420 (29),
   pancreatitis acute 193 (18), chronic 76 (2); cysts/pseudocysts 18 (2), other 133 (7).

13. **Liver — Cirrhosis** — 878 (211),
   cirrhosis 563 (89) - alcoholic 273 (121), - biliary 42 (1).

14. **Liver — misc.**, 1823 (328),
   abscess 14 (4), alcoholic 61 (8), Budd-Chiari 14 (3), chronic (unspecified) 112 (21), chronic persistent hepatitis 55, coma 230 (94), echinococcus 5 (1), hepatomegaly 5, hepatorenal 60 (43), jaundice 15, necrosis 103 (36), portal hypertension 102 (15), portal vein thrombosis 60 (12), viral hepatitis 805 (79), other 183 (12).

15. **Biliary,** 1278 (51),
   carcinoma 15 (2), cholecystitis 582 (6), cholelithiasis 278 (5), cholangitis 110 (11), cholangiocarcinoma 62 (7), obstruction biliary ducts 125 (12), other 106 (8).

16. **Gastroenteritis and other Small Intestine,** 1537 (99),
   gastroenteritis 384 (6), gastroenteritis bacterial 475 (32), - radiation 15 (1), - toxic 7; benign tumor 14 (1), blind loop 3, celiac 7, functional diarrhea 162 (6); ischemia 106 (27), malabsorption 98 (4), malignant 26 (1), perforation/fistula 116 (16), ulceration 15, other 209 (5).

17. **Enteritis, enterocolitis,** 544 (6),
   regional enteritis 135 (2), small intestine 198 (3), small and large intestine 116 (1), large intestine 95.

20. **Peritonitis,** 291 (20),
   peritonitis 280 (19), peritoneal malignancy 11 (1).

32. **Colon — misc.,** 370 (17),
   angiodysplasia 81 (3), benign tumor 137 (4), foreign body 5, hemorrhage 111 (10), megacolon 7, other 29.

Inpatients

In the last century and a half, annual admissions to The Mount Sinai Hospital each year have increased from 113 in 1855 to 47,929 in 1996. The diagnostic data go back only to 1860. Over this period the proportion of gastroenterological admissions decreased steadily from 14% of total admissions to 6% in 1995. However, the severity of gastroenterological cases, as assessed by their fatality, increased from 5% (compared with total mortality of 8%) in 1860 to 6% in the most recent decade (compared with the current all-case mortality of 3%).

The commonest admitting diagnoses in the early decades of Mount Sinai were similar to those in outpatients: gastralgia, (gastro-)enteritis and oropharyngeal diseases (Tables 3 and 4). In the later decades of the 19th century, these were overtaken by the proctological components of perianal disease, hemorrhoids and constipation. (Peri)typhlitis (later to be called appendicitis) increased from 1 patient in 1860, 7 in 1870, 9 in 1880, 15 in 1890, 217 in 1900 and 458 in 1906, falling to only 9 in 1995. Oropharyngeal disease declined rapidly, with only one admission in 1906 and two in 1995.

No patient was diagnosed as having gall bladder disease at Mount Sinai until 1875, but by the 20th century such patients were one tenth of all hepatogastroenterological admissions. Gastric carcinoma was and remains uncommon. In the mid-19th century, patients with colorectal carcinoma were admitted less than once a month, but have become more frequent and 4% of digestive admissions, partly from improved investigational techniques, and (probably) partly from a real increase in incidence. The frequence of colitis, as it became diagnosed separately from (gastro)enteritis-dysentery, increased in this century, so that patients with colitis now represent 10% of digestive admissions, second only to regional enteritis at 11% (see chapter 14). Other disease diagnoses such as autointoxication and visceroptosis suddenly appeared, rose to a peak within a decade, and then effectively disap-

TABLE 4

Commonest Hepatogastroenterological Diagnoses, 1855-1996, of Inpatients by Decade and as Percentage of All GI Diagnoses.

	1855-1866		1867-1876		1877-1886		1887-1896		1897-1906		1986-1995		1996*	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
GI Admissions %	553		932		2258		4179		6759		20,114		16,955	
Gastralgia/Gastritis	248	(45)	264	(28)	502	(22)	826	(20)	381	(6)	890	(4)	797	(5)
Gastroenteritis, Inf. Hepatitis, Worms	113	(20)	225	(24)	572	(25)	342	(8)	365	(5)	534	(3)	1690	(10)
Oropharynx	70	(13)	134	(14)	284	(13)	1477	(4)	99	(1)	29	(<1)	246	(1)
Anal / Hemorrhoids	40	(7)	113	(12)	403	(18)	1438	(34)	1278	(19)	315	(2)	331	(2)
Alcohol Excess	28	(5)	27	(3)	15	(<1)	9	(<1)	0	(0)	137	(<1)	1092	(6)
Peritonitis	18	(3)	26	(3)	77	(3)	96	(2)	71	(1)	154	(<1)	291	(2)
Constipation	5	(1)	7	(1)	46	(2)	205	(5)	173	(3)	132	(<1)	239	(1)
Typhlitis / Appendicitis	5	(1)	24	(3)	46	(2)	420	(10)	2211	(33)	76	(<1)	234	(1)
Gastric Carcinoma	3	(1)	8	(1)	33	(1)	56	(1)	233	(3)	258	(1)	178	(1)
Irritable Gut	3	(1)	19	(2)	10	(<1)	27	(<1)	45	(<1)	75	(<1)	144	(1)
Liver Cancer 1°	3	(1)	10	(1)	29	(1)	31	(<1)	67	(1)	183	(1)	292	(1)
2°					2	(<1)	4	(<1)			163	(1)	753	(4)
Liver Cirrhosis			11	(1)	40	(2)	46	(1)	71	(1)	1552	(8)	878	(5)
Liver — misc.			10	(1)	85	(4)	116	(3)	127	(2)	858	(4)	1823	(11)
Colitis			10	(1)	16	(<1)	168	(4)	172	(3)	1926	(10)	320	(3)
Colorectal Carcinoma			8	(1)	36	(2)	63	(2)	136	(2)	630	(3)	509	(3)
Esophageal — misc.			6	(1)	9	(<1)	4	(<1)	46	(<1)	1301	(6)	1443	(9)
Gastric Ulcer			3	(<1)	37	(2)	35	(<1)	96	(1)	733	(4)	490	(3)
Biliary			1	(<1)	28	(1)	80	(2)	589	(9)	1070	(3)	1278	(8)
Intestinal Obstruction			1	(<1)	2	(<1)	36	(<1)	112	(2)	651	(3)	1081	(6)
Esophageal Carcinoma			1	(<1)	7	(<1)	11	(<1)	76	(1)	84	(<1)	54	(<1)
Pancreas Carcinoma					2	(<1)	4	(<1)	15	(<1)	200	(1)	479	(3)
Duodenal Ulcer					1	(<1)	1	(<1)	11	(<1)	716	(4)	193	(1)
Autointoxication									190	(3)	0	(0)		
Pancreatitis									26	(<1)	856	(4)	287	(2)
Visceroptosis									16	(<1)	1	(-)		
Regional Enteritis											2202	(11)	544	(3)
Diverticulitis											1398	(7)	424	(3)
Hemorrhage - upper											1346	(7)	446	(3)
Hemorrhage - lower											130	(<1)	111	(<1)

* The 1996 data are for diagnoses in that year.

peared. No doubt, a historian of the 21st century reviewing Mount Sinai gastroenterology will consider similarly obsolete some of our current diagnostic labels, such as gastro-esophageal reflux disease, non-ulcer dyspepsia, biliary dyskinesia, irritable bowel syndrome and inflammatory bowel diseases.

The 1996 digestive data are presented in Tables 3 and 4 by diagnoses, and not as in 1855 to 1995 by individual patient, who may today have a dozen different diagnoses. Of the 16,955 hepatogastroenterologically coded diagnoses, 34% were hepatobiliary. The commonest gastroenterological diagnoses included 8% for esophageal miscellaneous (mostly gastro-esophageal reflux disorders); 5% for inflammatory bowel; 3% each for gastric ulcer, gastric miscellaneous (mostly gastritis and gastroduodenitis), colorectal and pancreatic carcinoma; and 3% each for diverticulitis and hematemesis from unspecified site. The number of upper gastrointestinal hemorrhages from specified or unspecified sites was 1072; that is, 6% of all hepatogastroenterological diagnoses.

The changes in absolute and relative frequencies of these diagnoses will be presented in the following chapters, which cover the individual disease groups.

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8

The Esophagus

Ellen L. Wolf, M.D.

Abstract

Original investigations and descriptions of the radiographic findings and techniques of evaluation of the esophagus and esophagogastric junction were made at The Mount Sinai Hospital by Drs. Bernard S. Wolf and colleagues in the third quarter of the 20th century. These included basic descriptions of peptic ulceration of the esophagus, the gastric lined esophagus, definitions of hiatus hernia, terminology of the esophagogastric junction, use of the barium pill and correlations of cineradiology with manometry. **Key Words:** Esophagus, radiology, motility, esophagitis, hiatus hernia, esophagogastric junction.

Dr. Bernard S. Wolf, chief of Radiology at The Mount Sinai Hospital from 1949 – 1977, and his colleagues made original investigations and descriptions of the radiographic findings in many esophageal diseases. In the 1950s, advances in fluoroscopy and cineradiography techniques allowed more detailed study of the esophagus and its motility, and allowed correlative study with esophagoscopy and manometry.

An increase in clinical interest in diseases of the esophagus, particularly in benign inflammatory conditions associated with hiatus hernia, led them to refine and amplify special procedures, maneuvers and technical factors designed to demonstrate such lesions. The consistency of the barium used for the examination of the esophagus was altered. Recommendations were made for patient positioning and the projections for routine studies and those for demonstrating particular diseases (1). They used a radiolucent bolster during continuous drinking in the prone right anterior oblique (RAO) position, to demonstrate minimal herniation of the esophagus and maximal size of the hernia (1, 2).

Various methods for demonstrating reflux were in use. However, Wolf's group recommended a more physiologic evaluation, with the patient in a moderate supine Trendelenburg position (1). It was noted that a fair amount of air was swallowed along with the barium, and by continued drinking through the straw after completion of a cup of barium, additional swallowed air would lead to a "double contrast" effect. This was the basis for the primary double contrast study in use today (1).

Peptic Esophagitis

In 1934, Winkelstein described to the annual meeting of the American Medical Association (AMA) a new clinical entity which he called peptic esophagitis (3). His five cases all had symptoms typical of the recently established disease of peptic ulcer of the esophagus, especially pain and dysphagia, but radiology showed only irregular narrowing, esophagoscopy only congestion and inflammation, and biopsies only acute and/or chronic inflammation; there were no ulcers. Three of the five had a previous duodenal ulcer, one a previous esophageal ulcer and one a subsequent incisural gastric ulcer. Acidities were high. All five responded to ulcer therapy and Winkelstein attributed the peptic esophagitis to erosion by gastric juice rising into the lower part of the esophagus. Similar cases were reported at the same time both in Europe and elsewhere in the U.S. The presence of a hiatus hernia was not emphasized in the 1930s, and it was only in the

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1940s that Allison attributed the esophagitis to reflux with hiatus hernia.

The 1950s saw the first basic radiologic descriptions of peptic ulceration of the esophagus (4–8). In 1954, Winkelstein, Wolf, Som and Marshak recognized that the triad of duodenal ulcer, hiatus hernia and peptic esophagitis is of special clinical significance (5). In 1957, Winkelstein presented twenty cases: "Peptic esophagitis probably commences with a more or less continual transcardial reflux from the stomach of a highly acid peptic secretion. This reflux may result from the hypersecretion associated with the duodenal ulcer or from the unexplained decrease in the tone of the cardiac sphincter. Perhaps the characteristic nocturnal hypersecretion with the patient in the horizontal position leads to prolonged bathing of the lower esophagus by the highly acid gastric contents" (8). Complications included stenosis, massive hemorrhage and perforation. Although Winkelstein continued to distinguish his peptic esophagitis from reflux esophagitis, it is the latter term or the more inclusive "gastro-esophageal reflux disease" which now prevails.

The radiographic findings in peptic esophagitis and peptic ulceration in association with gastric lined esophagus (Barrett epithelium) were described in detail in subsequent papers (9, 10). It had been stated previously that esophagitis occurs in one-half to three-quarters of patients with sliding hiatus hernia and that radiologic findings are frequently absent. Wolf and his colleagues identified subtle abnormalities that would suggest the presence of mild esophagitis, such as mild functional disturbances with inefficient peristaltic stripping action, mild nondistensibility and subtle fold and mucosal abnormalities.

Hiatus Hernia and the Esophagogastric Junction

The radiographic anatomy of this region was studied extensively and defined by Wolf and colleagues (2, 11–21). These descriptions were supplemented by many illustrations which captured the dynamic changes observed fluoroscopically in this region (2, 11–21). The terminology of the esophagogastric junction had long been disputed and correlations with anatomical and surgical findings were unsatisfactory. They were able to correlate radiographic observations and manometric measurements, and classified the rings seen in the distal esophagus as A rings (contraction) and B rings (the B rings representing the esophagogastric [EG] or squamomucosal junction). They then defined and redefined the radiographic diagnosis of sliding hiatus hernia.

Conclusions reached by studying large numbers of patients helped to clarify confusing terminology and correlated radiographic findings with manometric and autopsy descriptions of the EG junction. By 1958, it was possible to make the following authoritative conclusions (12) (Fig. 1):

1. The terminal two or three centimeters of the esophagus may contract and relax as a unit independently of the adjacent portions of the esophagus and stomach. Lerche's term, the vestibule (22), may be applied to this segment.

2. The vestibule as a single distensible unit can be observed only in the presence of a direct hernia, since the distal half of the vestibule normally is located in and below the diaphragm and is therefore limited in distensibility by extrinsic factors.

3. Notches or a static ring may be seen at the distal margin of the vestibule when the vestibule is herniated and distended. Since these notches indicate the junction between the vestibule and the stomach, their presence above the diaphragm is indicative of a hiatus hernia.

4. Notches or a complete ring may also be seen at the proximal margin of the vestibule. A ring in this location may show independent contractile activity and therefore may be equated with the inferior esophageal sphincter of Lerche. However, except perhaps during regurgitation, localized sphincter activity in this area is less commonly seen than contraction of the vestibule as a whole. The description of Lerche emphasized remarkable distensibility of the vestibule rather than the more important functional aspect of contractility.

5. The "high pressure zone" or "gastroesophageal sphincter" or "vestibular sphincter" described as a result of pressure studies in the esophagogastric region corresponds to the vestibule as described above.

6. In the studies reported, there was little or no evidence for the presence of a discrete sphincter at the distal margin of the vestibule, that is, at the cardia. It is possible, however, that the notches and ring seen

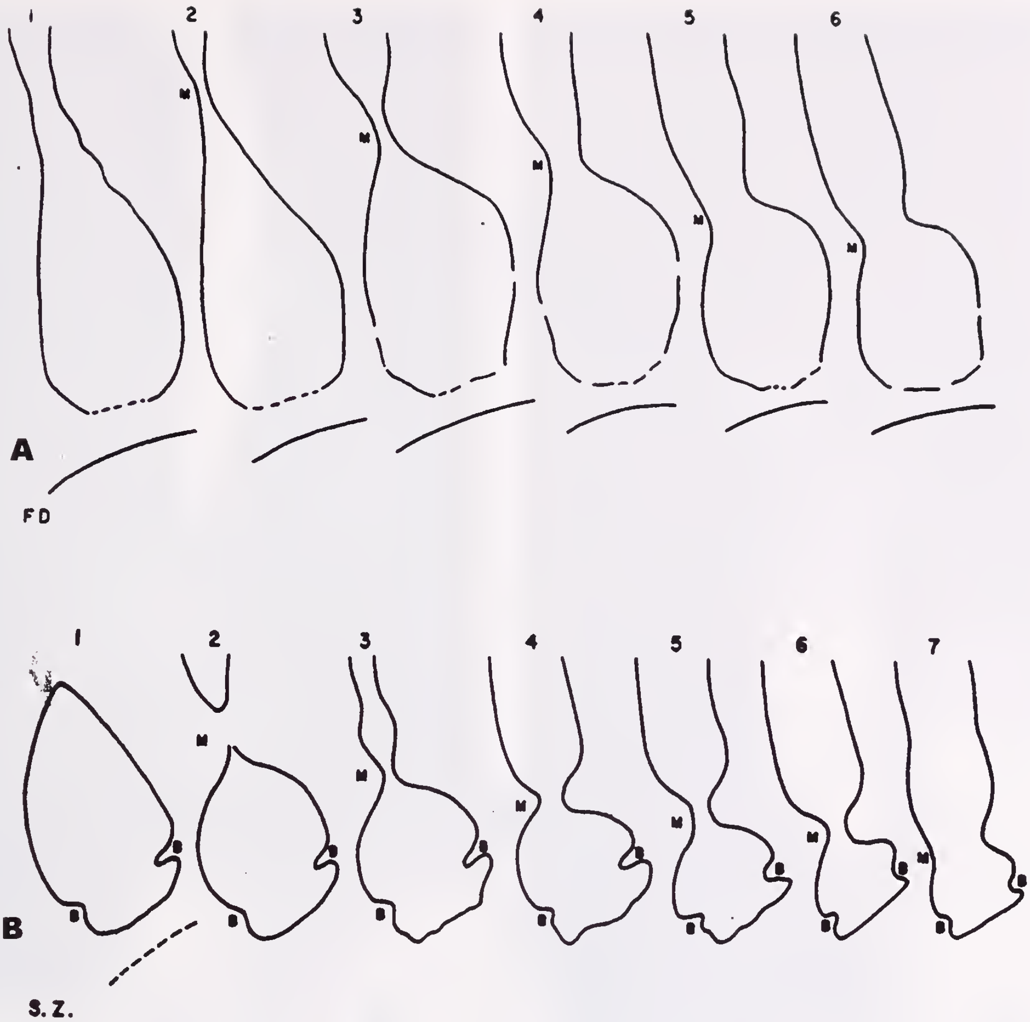

Fig. 1. The Gastroesophageal Vestibule. Reproduced with permission from *The Journal of The Mount Sinai Hospital* (12).

A. Tracings from a movie sequence showing the formation and change in size of the phrenic ampulla during maintained deep inspiration. The elongated constriction (M) represents the stripping peristaltic wave which is slowed up in the distal esophagus as it progresses into the ampullary formation and displaces barium proximally. Note that the width of this constriction increases as it progresses distally and that the wave stops about 3 cm above the diaphragm. The presence of a small hernia in this patient is not evident in these tracings but was suspected from other views. Faint notches about 2 cm above the diaphragm were occasionally seen in fleeting fashion.

B. In this patient, opaque material was injected into the wall of the esophagus down to the esophagogastric mucosal junction, confirming the presence of a small hiatus hernia beginning at the BB ring. Sequence of events during deep inspiration and the formation of the phrenic ampulla demonstrate that the BB ring remains unchanged in location while the constriction associated with the peristaltic wave (M) travels distally but stops 1 cm or so above the B level. Note complete cut-off at level of hiatus (dashed line in frame 1) despite the presence of a hernia.

in this area result from the existence of the specialized muscle bundles designated in the anatomical literature as the cardiac sphincter or the constrictor cardiae. The term "sphincter," however, appears to be a misnomer.

7. The beginning of gastric mucosa or rugae corresponds sufficiently well to the level of the so-called distal notches and ring seen on roentgen examination to make these equivalent criteria for the junction of esophagus and stomach.

8. The term "phrenic ampulla" was introduced into the roentgen literature by Templeton to apply to the sac-like collection of barium trapped above the diaphragm in deep inspiration. The phrenic ampulla, however, is not a unique structure since it

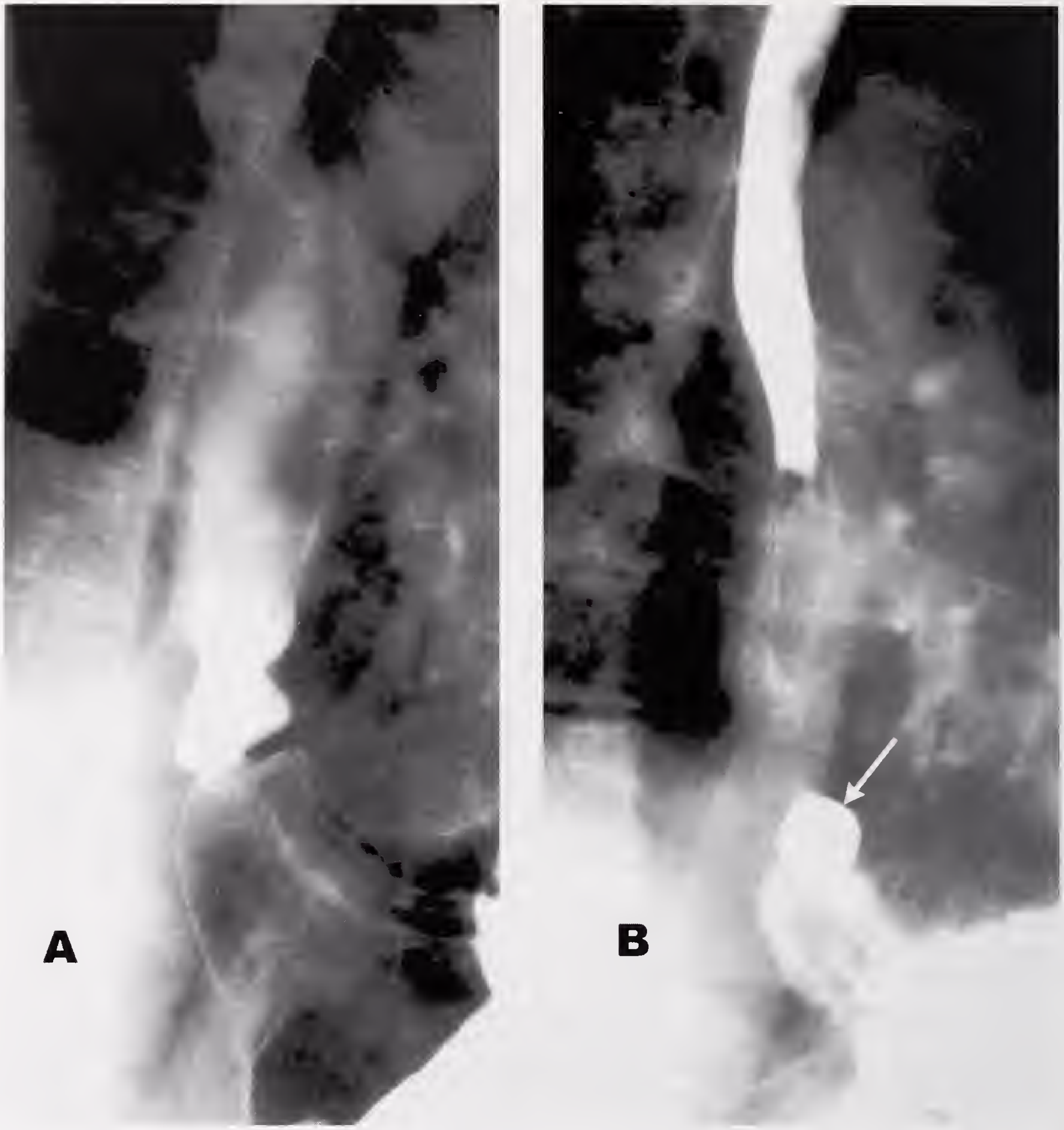

Fig. 2. Barium esophagram demonstrates (A) a hiatus hernia with A and B rings and (B) impaction of the barium pill (arrow) at the level of the ring. Symptoms could therefore be attributed to the ring.

> has a variable size determined by the pinchcock action of the diaphragm and the progress of the primary peristaltic wave. In the presence of a small direct hernia, the phrenic ampullae include the vestibule and the herniated portion of the stomach. The term "phrenic ampulla" as used by radiologists should not be confused with the original anatomical description, which presumably included features currently ascribed to the vestibule.

The first report of a B ring treated endoscopically was made in 1960 by Som, Wolf and Marshak (23). The patient had a symptomatic B ring, measuring 1 cm in diameter as measured in comparison with an impacted 1.25 cm barium pill. A 1.6 cm (48F) esophagoscope was passed and through it an esophageal forceps with right angle punch distally. The ring was grasped between the cutting jaws of the punch and severed. The patient had successful relief of symptoms.

The Barium Pill

In 1956, Wolf reported the use of a half inch barium tablet to detect minimal esophageal stric-

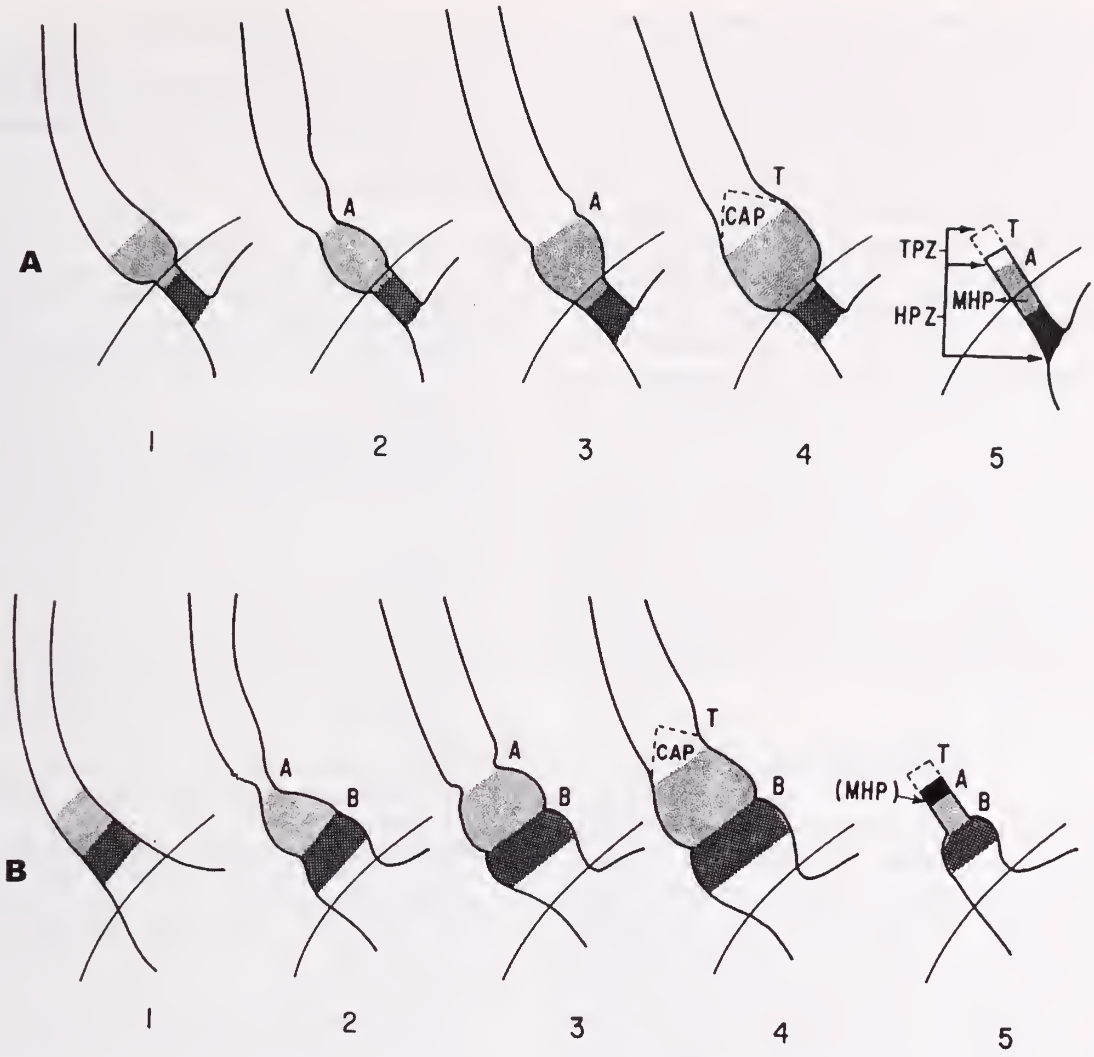

Fig. 3. The inferior esophageal sphincter. Reproduced with permission from the *American Journal of Roentgenology* (28).

A. Diagrammatic representation of vestibular and cardiac canal segments under normal circumstances in filled and empty phases. The vestibular segment is dotted and the cardiac canal cross-hatched. The proximal margin of the vestibule and the site of a potential functional ring is indicated by A. The cap in Panel 4 indicates the appearance in the transitional zone when the peristaltic wave reaches this area. Panel 5 represents the resting state. The transitional pressure zone (TPZ, unshaded) is shown as extending from the end of a tubular esophagus proper to the A level. The sharp distinctions in the resting phase diagram do not actually exist. The high pressure zone (HPZ) extends from the A level to the cardiac orifice. The peak or maximum pressure (MHP) of this zone is below the level of the hiatus.

B. Diagrammatic representation of the vestibule and "cardiac canal" in hiatal herniation. The A and B levels are indicated. The dotted region represents the vestibule and the cross-hatched regions the incompetent persistently dilated cardiac canal. The sling fibers which normally contract completely to form a short tubular segment now act as if they were part of the fundus of the stomach. Panel 5 shows diagrammatically the possibility that, in some cases, a discrete zone of resting, or maximum, high pressure zone may appear corresponding to an A ring. Pressure at this site may equal or exceed the maximum of the normal HPZ. The resting pressure in the vestibule itself may be somewhat higher than or equal to fundic pressure. In other cases, there is no region between fundus and tubular esophagus in which resting pressure exceeds fundic pressure, i.e., the cardiac canal and vestibule are incompetent and no compensatory A ring is present.

tures (24, 25). These tablets are often referred to as "Wolf pills." The assumption was that if a tablet of this diameter passes through the esophagus, dysphagia is not likely to be of an obstructive basis. The diameter of 1.25 cm was selected to correspond with the diameter of a 36F esophagoscope. The pill is of use in patients who complain of difficulty in swallowing but in whom no apparent or definite abnormalities are identified by conventional methods, and to confirm that findings such as rings or apparent strictures are indeed responsible for symptoms (Fig. 2). The pill is shaped so that obstruction is not increased even though the tablet may be prevented from passing. If obstruction is present and the pill is unable to pass through a stricture or a ring, it will disintegrate within 15–20 minutes. The pill is also helpful in identifying hypopharyngeal or cervical esophageal webs that may be overlooked in conventional studies. If a pill is impacted at that level, it is usually regurgitated after a short interval.

Motility Studies

Working in conjunction with the gastroenterologists, primarily Dr. Bernard R. Cohen, correlations with cineradiology and manometry of the pharynx, hypopharynx and esophagus were made (14, 16, 19, 26–28). More detailed and more physiologic understanding of the radiographic findings were possible using these techniques (Fig. 3). In 1960, intraesophageal pressure determinations were performed and correlated with the radiographic findings during the swallowing of barium using modifications of previously described techniques (14). The findings demonstrated that the junction of the phrenic ampulla and the narrow or "empty" segment in barium filling of the esophagus corresponds to the position of the hiatus and that the junctional segment therefore lies entirely within the abdomen. Refinements in the technique and additional observations were subsequently made, and a series of pressure inversion points were identified during the course of inspiration which corresponded to the posterior region of the physiologic hiatus (16). Manometric features were then correlated with the cineradiographic findings at the esophagogastric junction in patients with hiatal hernias and rings (18, 26–29). Clinical applications of esophageal motility studies and the radiologist's role in the evaluation of patients with heartburn evolved from these physiologic-roentgenographic studies (30, 31).

Conclusions

The radiographic techniques described above and the barium pill are still in wide use today, as are the definitions and terminology of the esophagogastric junction.

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Gastric Secretion

Jeremy Hugh Baron, D.M., F.R.C.P., F.R.C.S.

Abstract

The European gastric test meal was widely used in The Mount Sinai Hospital in the 1890s and early 1900s, but was then abandoned diagnostically after the introduction of gastroscopy and radiology. The fundamental methodological advances of Franklin Hollander led to his quantitative formulation of the ionic concentrations of the gastric acid parietal and nonparietal components, followed by his insulin test for completeness of vagotomy. **Key Words:** Gastric secretion, acid, biochemistry, components, insulin test of completeness of vagotomy.

In the last 150 years, measurements of gastric acid have developed from the test meal to measurements of basal, insulin-stimulated and maximal acid output.

Test Meals

Morris Manges (see chapter 3) brought to Mount Sinai the latest German concepts, equipment and tests in gastroenterology. He could not obtain an Ewald tube in the U.S. and had some made by the Davidson Rubber Company, 24 inches long, and in large sizes, 29, 31, 34 (French) gauge. He emphasized the precise details of intubation of the fasting patient for the Ewald Test Breakfast (a dry roll and a cup of hot water or tea) followed by evacuation of the gastric contents one hour later (1). Measurements were made by litmus paper, then titration with decinormal soda using Congo red and phenolphthalein as indicators for free and total acidity, with Uffelman's reagent for lactic acid (2). Manges saw little point in routinely testing for pepsin, rennet, ptyalin and other ferments (3).

On the basis of the hard data, Manges warned against routine use of test meals because "distinct pathological processes do not produce corresponding sharply defined changes in the chemistry of the stomach" (2). He considered the main value of the test meal to be in the differentiated diagnosis of gastric cancer when hydrochloric acid was absent and there was an excess of lactic acid (from fermentation in the stomach) (4).

Manges brought to Mount Sinai other new European diagnostic equipment. Einhorn's gastrodiaphane was a small incandescent lamp attached to the end of a stomach tube, allowing a red area to be seen normally on the abdomen giving some impression of the position and size of the stomach and colon (2). Bianchi and Bazzi's phonendoscope combined auscultation and percussion to ascertain the positions not only of the heart and lungs but also of the stomach, colon and even gall bladder (5).

Edward Aronson was assistant physiological chemist before being appointed as the first gastroenterologist at The Mount Sinai Hospital (see chapter 3). He came to Mount Sinai with considerable experience of the various test meals from Ewald's clinic in Berlin. One sophisticated test meal was the Sahli flour and butter meal, which allowed the fat to be used as a dilution indicator to calculate how much meal had been emptied into the intestine, how much remained in the stomach, and how much of the aspirated meal consisted of gastric secretion (6). A dilution indicator could therefore distinguish between hyperacidity and hypersecretion. However, the com-

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plexity of the test, the analyses and the calculations made the Sahli test impractical, and the Ewald-Boas meal remained in use at Mount Sinai until the 1950s. Another of Aronson's papers on gastric secretion (7) had an almost 18th century air, because it analyzed 81 samples of vomit, mostly post-anesthetic.

In about one in ten test meals, fragments of gastric mucosa large enough for histology were sucked into the tube. Boas had considered these specimens a means of distinguishing neurosis and a catarrhal condition (gastritis). Aronson found either congestion or gastritis in these fragments, but again the clinical utility was minimal (8). By 1912, Aronson was sharing Manges' disappointment with the diagnostic value of the test meal and was optimistic that the new techniques of gastroscopy and radiology would give better answers in due course (9).

Nevertheless, in 1915, 400 patients in the GI clinic still had a test meal each year, effectively "every patient in whom there is no contraindication to the passage of a stomach tube" (8). However, by 1916, Aronson was beginning to rely on the radiologic demonstration of a niche of barium or bismuth as pathognomic of an ulcer crater. Yet, "for the diagnosis of a simple gastric ulcer the . . . use of the stomach tube and stool examination gave much more information" (10).

Gastric Analysis

Measurements of Titratable Acidity

Prout (11) probably, and Jaworski and Gluzinski (12) certainly, used litmus as the indicator for their titrimetries. However, Ewald used either litmus or phenolphthalein as well as Congo Red paper to measure what was then called free acid. Once pH scales became available, it became possible to titrate to a specific end-point, but there was no agreement as to which single end-point, or whether to use two end-points, one for "free acidity" and one for "free alkalinity" ("total acidity").

The most comprehensive study of these methods of titrating gastric juice was made by Hollander in 1931 (13). Using a modified microburette allowing accuracy better than one percent (14), he found that while there was no difference in the acidities obtained by titration with phenol red (pH 6.8 – 8.4) and phenolphthalein (pH 8.3 – 10) for pure acid gastric juice from animal fundic pouches, this was not the case for human stomach contents which contained protein. In 1938, Hollander (15) showed that the mean difference in titratable acidity between the two indicators phenol red and phenolphthalein was 5 mmol/L (range 2 – 11), and concluded that "based on the theory of titration of buffer-containing solutions, there can be no doubt that an end-point of 7.0, precisely determined by comparison with a buffer standard, is more correct than an end-point of considerably higher pH value and determined by a gross color change." Hollander discussed electrometric titration, and "the simple and cheap commercial set-ups" which he lacked are now in routine use for his now universally accepted end-point of 7.0 or 7.4 as an alternative to colorimetric titration using phenol red.

Parietal and Nonparietal Components

A specimen of gastric aspirate is a mixture of the acid secreted by the parietal cells of the stomach, the alkaline juice secreted by the nonparietal cells, and contamination of these gastric components by regurgitation of intestinal, pancreatic and biliary secretions from below and by swallowed saliva from above. Both Heidenhain and Pavlov postulated an acid component of fixed ionic concentration. Hollander's two-component hypothesis (16) explained the varying composition of gastric juice by the assumption that two components of fixed ionic composition are secreted by the stomach in varying volumes, as opposed to the Teorell hypothesis of an exchange-diffusion of ions across the mucosa (17).

Hollander (16) postulated that "the parietal solution is essentially an isotonic solution of hydrochloric acid" and is admixed with an alkaline component of sodium chloride and bicarbonates (18), a buffer secretion of composition similar to blood plasma (19). Since then, there have been various formulas for calculating the acid parietal and alkaline nonparietal components, especially those of Fisher and Hunt (20), Hunt (21 – 23), Thompson and Vane (24), and Whitheld and Hobsley (25). After Hollander moved to Mount Sinai in 1936, he and his first research fellows, Penner and Saltzman, showed that the nonabsorbed phenol red (26, 27) was preferable to phenolphthalein as a dilution indicator in gastric analysis (28). Hollander had worked with Pavlov and Heidenhain pouch dogs from his time at Yale (29), and his unit now reassessed the evidence that the vagal innervation of the Pavlov pouch was intact: it was not (30), and they therefore designed a new stomach pouch without interruption of its vagal supply (31). They were then faced with the problem of differentiating those stomach pouches innervated by the vagus and those which had been denervated. They sought advice from seven experts, all of whom used the psychic and/or chemical stimuli of a meat meal, but found these tests unreliable (32). Hollander's group then devised a new stimulus, insulin hypoglycemia (32, 33), the future "Hollander Test." However, although the Heidenhain pouches were clearly denervated, the test did not distinguish "degrees of vagality" between the Hollander and Pavlov pouches.

Nevertheless, the Hollander test was used to assess the completion of vagotomy in six patients in Dr. Colp's service; all were incomplete with definite acid response to the insulin (34). The test then became "a standard routine procedure in [Mount Sinai] hospital for all cases in which a division or excision of the vagus nerves has been performed" (35), with a standardized protocol of 15 units of insulin injected intravenously after fasting gastric and blood glucose samples, followed by eight gastric samples collected at 15-minute intervals and three more blood samples during this two-hour period. Adequate hypoglycemia was defined as < 50 mg/100 mL but no precise levels of acidity were stated. Not all of the unoperated patients showed acidity rises, which were seen in all the unilateral vagotomy patients and in at least 10 of the 21 patients after bilateral vagotomy (35).

The subcommittee on vagotomy of the American Gastroenterological Association did a national survey concerning the gastric function tests used in connection with this operation. Hollander (36) recommended the overnight acid measurement and the insulin test, if performed, and the need to interpret the results by his criteria. Soon the "Hollander test" (an eponym disclaimed by Hollander [37]) was used universally, despite inconsistencies in technique and interpretation and the fact that there was no correlation between clinical results and postoperative insulin test data (38, 39).

Dose Response Relationships of Insulin Hypoglycemia and Gastric Acid

Hollander's group (32), in their original study, concluded that "it is impossible . . . to establish any quantitative relation between the magnitude of the insulin dosage or the hypoglycemia on the one hand, and the volume-rate of secretion or the acidity on the other." However, Jemerin, Hollander and Weinstein (33) claimed "a rough parallel between the degree of hypoglycemia and the magnitude of response that was obtained. . . ." This discrepancy may be related to Hollander's group having measured volume and acidity separately while omitting the calculation of their product, the acid output. When their data on dog 77 was recalculated (40), there was a significant inverse linear correlation of gastric acid output with the lowest blood sugar concentration, similar to the results in humans (41, 42), which established that insulin hypoglycemia provides a quantitative glycopenic stimulus producing quantitative vagal acid response (43). The criteria for an adequate insulin test in the unoperated subject were then established: "An insulin dose of about 0.2 U/kg may be optimum in producing sufficient hypoglycemia (blood glucose below 30 mg/100 mL; 1.7 mmol/L) to guarantee initiation of gastric secretion in an individual, to ensure a near maximal vagal acid output, but not to allow blood glucose to fall so low (< 15 mg/100 mL; 0.8 mmol/L) that hypoglycemic inhibition of gastric secretions or dangerous side-effects be produced" (43).

The insulin test became an essential tool for the assessment of the vagotomies (truncal, selective, proximal gastric/highly selective), which became for almost half a century the most frequently performed operation to reduce acid secretion. It was shown that in patients before (40–42) and/or after vagotomy (44–46), the same dose of insulin, 0.2 U/kg, was found optimal. In the last twenty years, potent acid inhibitors, and then eradication of *Helicobacter pylori*, replaced surgery in the elective treatment of peptic ulcer.

However, even when Hollander's qualitative acidity criteria were replaced by quantitative acid measurements, more than a dozen alone or in combination were recommended to refine the interpretation of the test (43). These absolute criteria were all based on a common fallacy, that an insulin test gave a positive or negative answer, and that vagal innervation is either present or absent. We no longer accept, as Dragstedt did (47), that insulin-stimulated gastric acid after vagotomy is an all-or-none phenomenon, with acid secretion unchanged if a single vagal fiber remains intact. We no longer assume that a surgeon cuts either all or none of the vagal fibers to the stomach. Nor do we accept Hollander's denials that an acidity increase is an indicator of the number of intact vagal fibers, i.e., "degrees of vagality" (33).

Instead we believe that "If peak acid output after insulin in the intact stomach represents the sum of the secretory output stimulated by the individual vagal fibres, then the reduction in insulin-stimulated peak acid output after a vagotomy is an index of the proportion of efferent vagal fibers which have been divided" (43). The final methodological advance was to correct measurements of insulin-stimulated secretion for pyloric loss and duodenal reflux by Hobsley's formulas (48).

It is now accepted that Hollander was correct in believing that the insulin test should not be used in the individual patient to predict who will develop or has already developed recurrent ulceration after vagotomy, nor which patients with recurrent symptoms have indeed re-ulcerated. However, Hollander's insulin test, and its safer successor, sham-feed, chew and spit, often supplemented by measurements of basal and pentagastrin-stimulated acid, were once essential tools in the systematic assessment of the various vagotomies and of different vagotomists (49), and in the evaluation of residual innervation in patients with recurrent ulcer, in order to plan revision surgery (re-vagotomy and/or antrectomy) (49).

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10

Acid Secretion after Gastric Operations

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Abstract

In the early 20th century, the commonest surgical treatment of peptic ulcer was gastroenterostomy. Crohn and Wilensky demonstrated that this operation did not achieve its aim of markedly reducing gastric acidity or of accelerating motility. These results were highly controversial, but led to Lewisohn visiting Haberer in Austria in 1922, and convincing Dr. A.A. Berg to abandon gastroenterostomy and use partial gastrectomy as the standard ulcer operation, with additional vagotomy in those patients with duodenal ulcer with high acidity. In 1929, a few patients were treated by vagotomy and gastrojejunostomy by Dr. Ralph Colp, with discouraging results. It was only in the 1940s that Mount Sinai surgeons adopted transthoracic or subdiaphragmatic vagotomy and gastroenterostomy (or later, pyloroplasty) as their standard, effective acid-lowering treatment of peptic ulcers. **Key Words:** Gastric acid, gastroenterostomy, partial gastrectomy, vagotomy, pyloroplasty.

IN 1916, CROHN, REISS, AND WILENSKY began studies on gastric acidity after gastroenterostomy (1), using a heavy oatmeal gruel test breakfast (2) and motility by kymography (3). Neither test was novel, but the results of their studies on 37 patients, on whom Dr. Berg had performed a posterior retrocolic gastrojejunostomy, were new and important. The patients were divided into three groups. Group A consisted of 11 patients with few or trivial symptoms and Group B consisted of 14 patients who had developed new symptoms after their operation. Seven patients of the 12 in Group C had similar symptoms to Group B, but 2 had developed gastrojejunal ulcers and the other 5 had stomal constrictions. Wilensky and Crohn were careful, however, to point out that most of the patients were examined because of their symptoms and did not constitute a representative selection of patients after gastrojejunostomy. Their results suggested that this operation did not achieve its aim of markedly reducing gastric acidity or of accelerating motility.

Around the same time, Dr. William Mayo was making one of his regular visits to Mount Sinai; he was invited to the laboratory by Libman to listen to these results. This prompted an invitation to Crohn and Wilensky to present a paper at the American Gastroenterological Association (AGA) in Atlantic City in May 1916, where it was well received by a standing ovation, according to Crohn (4).

Standing ovation or not, the discussion was critical and occupies ten pages of the published transactions (5), although it is not appended to the later paper (which does however provide graphs and kymograms) (1). Some discussants (5) claimed that in their centers, 85–90% of their patients "have been injudiciously chosen for operation and various surgeons good and indifferent have performed them." Others advised pyloroplasty rather than gastroenterostomy. One speaker cited a non-American authority, Mathieu in Paris, where "very few, if any, of their cases of gastro-enterostomy, if followed over a sufficiently long time, failed to show some pathological symptoms, gastric or intestinal." Crohn's lengthy reply to his critics was so diplomatic that he was

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elected a member of the AGA in 1918 on the recommendation of Max Einhorn, Jacob Kaufman and Morris Manges (6). He became the first staff member of The Mount Sinai Hospital to serve as president of the AGA, from 1932 to 1933.

Despite the preaching by Manges and Aronson that the fractional test meal should not be used as a routine test, it was still so used (5). The use of such tests caused prolonged discussions on the postulated diagnosis of gastric hypersecretion (gastrochronorrhoea) (5), which in retrospect was clearly a non-diagnosis, since the test meal only provided qualitative measurements of gastric acidity. Quantitative measurements of juice volume, basal or stimulated, were yet to come (6).

Partial Gastrectomy

In 1922, Lewisohn returned from visiting Haberer in Innsbruck, Austria, with details of the new operation for peptic ulcer, namely partial gastrectomy, to replace gastroenterostomy for duodenal ulcer because of the unsatisfactory results seen in Europe after this drainage procedure (7). Lewisohn convinced Berg to change his practice, and Berg was soon able to perform hundreds of these new operations, because he operated mornings and afternoons six days a week, and sometimes on Sundays. Clinical efficacy was measured by meticulous follow-up involving Social Service. The physiological effects consisted of the anticipated abolition of postoperative free acidity in almost all cases, together with increased gastric emptying.

Thus, Lewisohn and Feldman (7) were able to persuade 88 patients to have a repeat Ewald test meal years after their gastric operations. They were the only patients to consent from the 191 surviving patients (out of a total of 213) who were operated on at Dr. Berg's service between 1915 and 1920. Simple gastroenterostomy (n = 13) changed acidity little and never abolished free acid; even with pyloric exclusion in addition (n = 50), only 2 patients lost their free acid. However, after partial or subtotal gastrectomy for gastric ulcer, free acid persisted in only 2 patients, and after gastrectomy for gastrojejunal or recurrent duodenal ulcer, each of 8 patients lost free acidity (7). Klein confirmed the different results with the various types of peptic ulcer (8). Every patient with a gastric ulcer lost free acid within 6 months of partial gastrectomy, compared with only one-quarter of patients with duodenal ulcer and one-half of those with gastrojejunal ulcers. These data were cited by Berg in his classic 1930 paper (9), which finally convinced the next generation of American surgeons that subtotal gastrectomy was the rational and effective operation of choice for peptic ulcers. An update in 1933 by Winkelstein (10) of 122 patients after partial gastrectomy showed absence of free acidity in 55% of patients who originally had a duodenal ulcer, but in 88% of those operated on for gastric ulcer.

Ulcer Recurrences at Mount Sinai and the Jewish Question

Critical reassessment of gastroenterostomy at The Mount Sinai Hospital, begun by Wilensky and Crohn in 1916 (5), and continued by Berg's group in the 1920s, met with considerable opposition by advocates of the then-standard operation, both at Mount Sinai (4, 11) and elsewhere (12, 13). Surgeons claimed that "their" patients did well after "their" operations: "I have been able to follow 60 cases from 12 years to $3^1/2$ months. . . . In 88.33%, the result was satisfactory" (12). From 1905 – 1922, the Mayo clinic performed 7000 operations, but saw only 37 patients with recurrent gastric or duodenal ulcer (13).

Thus, the bad results at Mount Sinai were blamed not on the operation but on the poor selection of cases and/or poor operative techniques. However, the most bizarre explanation was Woolsey's attribution of the high Mount Sinai recurrence rate to their high proportion of Jewish patients (12), citing Eusterman from the Mayo Clinic: "There is a third type of case in which there is a tendency toward recurrence, in some instances repeated, over a short period. The Hebrew and the person with a hyperirritable nervous system who smokes excessively are illustrative of this type" (13).

Lewisohn rejected these disparaging suggestions to explain the high Mount Sinai gastrojejunal ulcer rate of 34% (14). "The large percentage was explained by the accuracy of our follow-up system, which included very careful personal examination of the patients."

Lewisohn submitted this question to Haberer and received the following answer: "The statement that gastro-enterostomy is followed by worse results in Jewish than in other patients is absolutely incorrect. I have among my patients less than 2 per cent of Jews; among those there are a number of gastrojejunal ulcers. These patients are as healthy today, following a subtotal gastrectomy, as the Gentile patients. I have never noticed any difference as to operative results between Jewish and Gentile patients. Professor Raffaele Bastianelli of Rome told me recently that he was under the impression that 25% of his gastro-enterostomy patients developed trouble, probably as a result of gastrojejunal or jejunal ulcers. He states that there are almost no Jews among his patients."

Vagotomy

Nevertheless, there were still patients with duodenal ulcer who developed jejunal ulceration even after partial gastrectomy, so that in 1938 Winkelstein and Berg (15) reconsidered the operative approach with their hypothesis that the problem lay with patients with high preoperative acidity. They found that patients with gastric ulcer or with duodenal ulcer with preoperative normal free acidity (20–40 mmol/L) had postoperative low or nil free acidity and negligible ulcer recurrences. Those with duodenal or juxtapyloric ulcers with high preoperative free acidity (> 60 mmol/L) were the group in which postoperative recurrent jejunal ulcers occurred, because of inadequate reduction of acidity. Recalculation of the data in their chart V shows that 13 patients who later developed jejunal ulcers had a reduction of free acidity from a mean and range of 76 (24–130) only to 61 (20–110) mmol/L after the partial gastrectomy.

The new Mount Sinai protocol (which Winkelstein [16] states was the idea of Dr. Eugene Klein) was to add subphrenic anterior vagotomy to partial gastrectomy in patients with duodenal ulcer with high free acidity (> 60 mmol/L) (15). After this operation, in a group of 31 patients, free acidity disappeared immediately in 16 and within months or years in another 10; all 26 remained well after 4–9 years' follow-up. However, there were 5 patients whose free acidity was not abolished by the new radical operation, but was reduced immediately from a mean (range) from 96 (74–135) to 25 (20–36) mmol/L, and within months or years to 23 (10–30) mmol/L; these 5 were without recurrences for up to 6 years (15).

According to Winkelstein, he had speculated in 1929 that if the addition of an anterior vagotomy to a partial gastrectomy further reduced acidity, then gastroenterostomy plus vagotomy should be tried for duodenal ulcer (16): "This operation was then carried out on the service of Drs. Berg and Lewisohn in two cases of rather severe duodenal ulcer with pyloric obstruction (one case operated by Dr. S. Hirshfield and the second by Dr. P. Klingenstein)." In case 1, free acidity was reduced from 70 to 10 mmol/L at 2 months after operation and at 3, 4, 5 and 7 years were 10, 0, 20 and 60 mmol/L, respectively. In case 2, acidity was reduced from 50 to 10 mmol/L at 3 months after the operation and after 3 and 4 years were 40 and 10 mmol/L, respectively. Both patients remained well. Three other patients were treated similarly, but no follow-up was reported (17).

These patients operated on in 1929 were probably the first patients with duodenal ulcer to be treated by vagotomy and gastrojejunostomy to reduce their gastric acidity, as distinct from reducing their pain by cutting vagal afferents. Two further patients were studied at Mount Sinai by Klingenstein on Dr. Colp's service. In one, in 1942 (case 6 of Weinstein et al. [18]), posterior gastroenterostomy and anterior vagotomy had little effect on alcohol- and insulin-stimulated acid. With the other patient, in 1939, there are discrepancies between the descriptions of case 5 of Weinstein et al. (18) and the case report of Cornell (19) as to whether the patients ever had duodenal ulcer. The latter patient was published (19) as "probably the first known case of attempted 'complete' subphrenic vagotomy for duodenal ulcer performed without any other operation." There were marked motor effects (no gastroenterostomy was added) but the acidities were little altered. Clearly, only partial vagotomy had been achieved.

Thus, deliberate partial vagotomy had been mostly unsuccessful in reducing gastric acidity; the one attempt at complete vagotomy had also been unsuccessful in lowering acid. Moreover, the Mount Sinai surgeons were reluctant to attempt the rational transthoracic or subdiaphragmatic vagotomy because of the added risk (18). After Dragstedt's epoch-making supradiaphragmatic bilateral vagotomy in 1943, Colp's group (20) reported 101 poor-risk patients with duodenal ulcer in whom gastroenterostomy and vagotomy led to an operative mortality of 5% compared with 0.7% for subtotal gastrectomy. Moreover, the recurrent ulcer rate was 15% for gastroenterostomy alone, 10% for gastroenterostomy and vagotomy, 8% for subtotal gastrectomy, and 0.6% for subtotal gastrectomy and vagotomy.

Nevertheless, Dragstedt's truncal vagotomy, or the later selective or proximal gastric (highly selective) vagotomies, became the standard operation for reducing acid in patients with ulcer for the rest of the 20th century. The operation of truncal vagotomy and pyloroplasty was used extensively at Mount Sinai from 1959 (21), with 76% mean reduction of maximal histamine-stimulated acid (22). Thus, over these decades, Mount Sinai had produced evidence that the efficacy of operations for ulcer was related to their acid-lowering results, allowing later gastroenterologists at Mount Sinai to aim at healing ulcers by acid-lowering drugs (see chapter 14).

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11

The Gastric Mucosal Barrier

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Abstract

Most gastroduodenal ulcer disease results from a weakness in the normal gastric mucous barrier against the penetration of acid secreted by the stomach. Based on meticulous and insightful research, the distinguished physiologist Franklin Hollander hypothesized that the stomach is protected against its own acid secretion by a dynamic two-component mucus-mucosal barrier. Hollander and his co-workers defined the physical and chemical characteristics of the mucus components of this barrier, as well as the defense provided by the surface epithelial cell layer, which he viewed as the second line of defense (the second component). Barrier investigators at Mount Sinai demonstrated the effects of impairment of barrier function with resultant increased back-diffusion of acid, and they defined the consequences of this acid penetration into the gastric epithelium. The contribution of these workers included important observations on the natural impermeability of the gastric corpus and fundus as well as the normally increased permeability of the antrum. They also presented evidence on the role of bile in duodenogastric reflux in gastric ulcer disease and the presence of impaired barrier function in patients with gastric ulcer and pernicious anemia. Further studies included demonstration that stress and carcinogens could disrupt the gastric mucosal barrier. Disruption of the barrier, in turn, was shown to allow carcinogenesis to occur by permitting the absorption of certain carcinogens which otherwise are warded off by the barrier. The Hollander two-component gastric mucosal barrier hypothesis has, in recent years, been increasingly validated by experimental data coming from other laboratories. **Key Words:** Gastric mucus, gastric mucosal barrier, gastric epithelium, gastric acid.

The Gastric Mucosal Barrier

It is now generally agreed that almost all gastroduodenal ulcer disease results from an abnormality in the mucosal barrier. In recent years, attention has focused on *Helicobacter pylori* and ASA/NSAIDs as important causes of this failure of barrier function. Uncommonly, ulcer disease of the upper GI tract is attributable to excessive secretion of hydrochloric acid rather than to a primary failure of the barrier itself.

Background

An early hypothesis on the inherent resistance of the stomach to autodigestion was that of John Hunter in 1772 (1). On observing the rapidity of post-mortem gastric autolysis, he ascribed the ability of the stomach not to digest itself during life to the presence of a "living principle." This "living principle" depended, in Hunter's view, on the continuing circulation of blood through the gastric tissue. In 1853, Virchow (2) refined this hypothesis, proposing that the acid in the gastric juice diffused back into the mucosa, where it was neutralized by circulating alkaline blood. Gastric ulcers were considered to be secondary to a restriction in local blood supply, with resultant ineffective neutralization of absorbed acid, leading to localized areas of autodigestion. Pavy agreed, publishing strong endorsements in 1863 (3) and 1869 (4).

Beaumont's epic observations provided a meticulous account of the dynamic nature of the gastric lining of his patient, Alexis St. Martin, a gunshot victim with an open gastric fistula (5). Beaumont described the inner lining of the stomach to be "constantly covered with a very thin transparent viscid mucus lining the whole interior of the organ." Beaumont documented this mucus layer to be a distinct alkaline entity of widely varying appearance and physical characteristics,

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often dependent on the general state of his patient.

An earlier reference to the protective quality of the gastric mucus layer itself was published by Glover in 1800 (6). Glover believed the function of the mucus to be "lubricating and that it must likewise defend the internal surface of the stomach and the intestines from the action of the gastric juice." Some 60 years later, Harley (7), who is usually credited with the initial hypothesis regarding the protective nature of the mucus layer, stated: "It is chiefly, if not solely, the mucus which protects the stomach from the chemical action of its own gastric juice." In 1855, Claude Bernard (8) recognized the apparent impermeability of the gastric lining to pepsin. Bernard also pointed out the importance of the dynamic quality of this gastric surface epithelium: "the epithelial layer is destroyed and renewed with great ease."

Bernard described the gastric lining: "The epithelium of the gastric mucosa, especially the glutinous mucus which covers the inner wall of this viscus, and which is seen very well when one opens the living animal, encloses the gastric juice as in a vase as impermeable as though it were made of porcelain." This view regarding the one-component nature of the protective barrier dominated physiologic thinking until the 1940s, when the importance of a dynamic two-component barrier was proposed by Hollander.

Hollander's Two-Component Barrier

During the first half of the 20th century, the prevalence of peptic ulcer disease increased alarmingly. The thinking of most clinicians and investigators turned to excessive secretion of HCl as the major causative factor in this disease. However, despite this consensus, Hollander proposed that the stomach's primary defense against peptic ulcers was the mucus-mucosal barrier. Hollander's insight into the functioning of the mucus-mucosa as a virtually impenetrable barrier to the acid which the stomach itself secretes grew out of his fundamental studies on the mechanism of gastric acid secretion. It became apparent to him, early on, that the parietal cell secretion consisted of nearly pure concentrated HCl; he was able to demonstrate that it remained almost unchanged within the gastric lumen over long periods of time. He also pointed out that peptic ulcer is a localized disease, rather than one diffusely affecting the gastric or duodenal lining, i.e., if hypersecretion of the acid were the sole cause of ulcer disease, then that disease should be more diffuse. He also drew attention to the fact that most individuals with hypersecretion of acid did not suffer from peptic ulcer disease and that many patients with peptic ulcer disease did not demonstrate hypersecretion of acid. To Hollander, the conclusion was obvious: some localized defect or weakness in the protective mucus-mucosal barrier must be primary in the causation of peptic ulcer disease. By 1944, Hollander presented his early ideas of the "mucous barrier" as a two-component, self-renewing system.

Franklin Hollander

Franklin Hollander had come to The Mount Sinai Hospital as director of the Gastrointestinal Physiology Research Laboratory in 1936, and he continued there until his death in 1966 (see above, chapter 6). His studies on gastric physiology began a decade earlier in the laboratory of Lafayette Mendel at Yale. In all, he published a total of 272 scientific papers. His final days were spent painfully but quietly at home, continuing almost daily meetings with those of us whom he was guiding through ongoing studies on gastric pathophysiology. In accordance with his request, his name did not appear on any papers published after his death. Hollander devoted the bulk of his time and energies to basic science rather than to clinically oriented research, yet he was always looking for direct clinical applications of his work and gave generously of his time and support to clinicians and trainees. It was Hollander's conviction that a grounding in bench research and in basic gastrointestinal physiology was essential to the development of the complete gastroenterologist.

In his earliest publication (9), Hollander reported that gastric juice collected from isolated canine gastric pouches had a pH of less than 1, provided special care was taken to avoid irritation of the pouch during collection of juice, thereby avoiding any stimulus to the stomach to secrete diluting or neutralizing substance. Hollander's new technique involved the construction of a sphincter at the mouth of the pouch. Although he left it unstated at the time, Hollander later referred to this observation as a crucial one, indicating to him that there must be very little (or virtually no) loss of acid via back-diffusion into the mucosa; otherwise, such low pH values could not have been achieved. When he published this observation in its final form (10), Hollander was able to report the pouch juice to have a constant pH value of less than 1.

His early interest in the barrier was already apparent in 1929 (11). Commenting on the high concentration of hydrochloric acid in the gastric secretion, "about 0.15 N.," Hollander stated: "Even more remarkable are the intracellular organizations which permit the existence of living normally functioning tissue in intimate contact with so corrosive a liquid. True, the fluid contents in the lumen of the stomach is much less acid, by reason of the neutralizing action exerted by food stuffs, saliva, and regurgitated intestinal juices. Nevertheless, even this less acid fluid will exert a marked digestive action on many tissues which may be immersed in it, even though these tissues are living organs transplanted into the stomach. The acid secretion, however, unaffected by admixture with the above-mentioned alkaline fluids exerts no such corrosive action on the cells which are immediately concerned in its elaboration. While the effective agent in the protection of these cells may be the mucus, no one has yet conclusively demonstrated that it is so, and thus, the stability of these tissues in the presence of digestive juices which they themselves manufacture remains as great a mystery as ever."

In the 1930s, Hollander continued his studies on the nature and mechanisms of gastric acid secretion (11 – 19). His observations refined and extended the views of Pavlov, and he formally proposed a two-component acid secretory process: (1) the parietal cell secretion, containing isosmotic HCl (160 mM) and no other ions except for "perhaps a little potassium," and (2) an alkaline component comprised of mucus, enzymes and a transudate of interstitial fluid. These were conceived to be relatively invariant physiologic entities with all alterations in the concentrated (isosmotic) primary HCl secretion resulting from dilution and neutralization by the non-parietal cell alkaline component. Absorption or back-diffusion of H^+ was, in Hollander's view, not a factor.

The major evidence supporting an opposing viewpoint was presented by the renowned physiologist Torsten Teorell (20, 21). Based on experiments in pylorus-ligated cats, as well as in an *in vitro* membrane preparation, Teorell concluded that the hydrogen ions of strong acids diffuse out of the stomach quite easily, and that this hydrogen ion loss occurs via an exchange diffusion for Na ions across the surface mucosa. He viewed the gastric mucosa as an ion exchange membrane whose function it was to reduce the intraluminal gastric acidity. Teorell's back-diffusion model received some support (22). One of the more interesting aspects of Teorell's 1939 report (21) was his observation that weak acids disappear from the stomach even more rapidly than do strong acids, a phenomenon ascribed to entry of un-ionized acid molecules via paths (solution in the cell membrane) other than those open to ions. The inflammatory effects upon the mucosa of the entry of these weak acids were noted, but better appreciation of their significance awaited the work of later investigators (23).

Hollander (24) objected to Teorell's hypothesis: "The notion that the concentration of HCl within the stomach may be reduced by a physical process of absorption is one which as yet has not acquired many adherents." Hollander pointed out that Teorell had not demonstrated directly the existence of an ionic exchange in the mammalian stomach, but rather had utilized *in vitro* non-vital membranes, as an "analogous" model. Hollander held Teorell's views to be "worthy of consideration and even of experimental examination," but they received little of either by that time.

Hollander's own early observation that highly acidic gastric secretions can be retained within canine gastric pouches up to 9 hours without any significant diminution in acidity cast considerable doubt on the likelihood of any such process of absorption or ionic exchange (12).

Hollander's studies on the physical and chemical properties of gastric mucus began with publication of an abstract written with Robert Felberg in 1941 (25). In it, they stated that "previously published data on mucus are too scant and divergent to yield criteria of purity of the secretion or quantitative correlations among its chemical characteristics," and then described their earliest efforts to obtain mucus secretion from canine fundic pouches. The abstract ends with: "these studies will be extended"; and, so they were.

In 1943, Hollander and Stein published their first joint paper on some of the characteristics of gastric mucus (26). They reported that a major part of the mucus secreted after pilocarpine administered is squeezed out of the surface epithelial cells by muscular activity. In particular, they saw oozing of blood from the mucosa after pilocarpine, a finding later featured in a study by Davenport (23). Seven years later, Janowitz, Hollander and Jackson (27) found that topical application of acetylcholine resulted in secretion of alkaline, cell-free mucus, confirming Hollander's previous conclusion that the exfoliation of gastric-surface epithelial cells is not an essential part of the process of mucus secretion.

Hollander first mentioned a "two-component barrier" in 1941 (28), when he suggested that such a barrier provided laboratory animals with their normal resistance to the induction of gastric cancer by topical application of carcinogens. He presented his concept of the barrier more formally in an editorial in *Gastroenterology* in 1944 (29) "Mucous secretion (including desquamation of affected surface mucosal cells) constitutes the most effective protective agent for the healthy mucosa — against tumor formation, as well as peptic ulceration. Some such modification in (mucus) secretory activity may obtain in the human precancerous stomach."

Hollander amplified this view in 1945 (30): "The one aspect of gastric physiology that might prove to be of fundamental importance in relation to gastric carcinogenesis is mucus secretion. This importance derives from its function as a protective agent against all forms of irritation, but particularly the chemical ones. Hence, any deficiency in output of mucus or in its essential physical properties might well serve to predispose the gastric mucosa to attack by an exogenous carcinogenic agent. This barrier involves not only the viscous mucus secretion, but also the mucous cells themselves. Mildly irritating solutions result in a flow of thick, jelly-like mucus. Histologic examination smears reveal considerable quantities of desquamated columnar epithelium. Spontaneous secretion, to the contrary, is frequently free of such desquamated columnar cells. . . . Obviously, if any cancerous change is induced, when these columnar cells make contact with a carcinogen, it will immediately elicit a shedding of these cells so affected making the development of an adequate tumor impossible."

Seeking confirmation of this view, Hollander and co-workers studied the effects of mild irritants and noted that the occurrence and volume of mucus and of desquamated surface epithelium increased with the irritating power of the agent applied (31). Hollander credits Pavlov (32) with stating that the copious flow of mucus after application of irritants to the gastric mucosa does not reflect serious pathologic condition but only a normal physiologic reaction to an irritant which "wards off danger which threatens the more important elements of the mucus membrane beneath."

Hollander and Lauber, studying multiple stimuli, found that clove oil water emulsion is the most effective stimulus of gastric mucus secretion (33). However, clove oil is a mixture of several compounds, including 80% eugenol (4-allyl-2-methoxyphenol). Therefore, they investigated pure eugenol as a topical stimulus and concluded that it is as effective a stimulus as clove oil and "has the advantage of being a single chemical individual." After exhaustive studies on the effects of many irritants and other stimuli, Hollander proposed that eugenol be adopted as a standard stimulus for study of the gastric mucus (34).

Hollander and co-workers explored the effects of repeated eugenol instillation in isolated canine gastric pouches (35). In these "fatigue experiments," striking changes occurred, with an initial flow of opaque jelly-like mucus decreasing, to be replaced by large volumes of secretion of clear alkaline fluid. These studies formed the basis for the later works of Code (36) and Davenport (37). In a companion paper (38) with Sonnenblick and Sober, Hollander documented cytologically the progressive desquamation of layers of epithelium after eugenol.

Hollander and Goldfisher (39) then described (by histology) a remarkably rapid 3-stage regenerative process after repeated eugenol applications: (1) the preliminary resurfacing of the denuded mucosa with flat cells, evident 30–60 minutes after removal of eugenol from the pouch, (2) the transformation of these new cells into low and tall columnar cells, and (3) the reformation of crypts in these areas of smoothly resurfaced mucosa. This entire process occurred within 36 hours following deep shedding of the mucosa as far down as the bottoms of the foveolae.

The definitive paper by Sober, Hollander, and Sonnenblick on the effects of topical eugenol application (40) established a new experimental approach to some stomach diseases — notably gastritis, peptic ulcer and carcinoma of the stomach. Hollander and co-workers looked at the possible beneficial effect of topical application of eugenol to the gastric lining of patients with peptic ulcer via increased mucus secretion (41). Ten out of 14 patients had complete or partial relief of symptoms, suggesting that prolonged stimulation of mucus secretion might be beneficial.

Formulation of the Two-Component Barrier Theory

After a decade of study on the nature of the gastric mucus and the underlying epithelium, Hollander formally proposed the concept of a two-component, self-regenerating barrier (42). According to his hypothesis, the gastric mucous barrier is a composite of two integrated structural units. The layer of viscous mucus constituted the first line of defense and the second was the layer of columnar and cuboidal cells of the surface of crypt epithelium. "The mucus layer constitutes a first line of defense in the gastric wall by reason of its tenacious adherence to the underlying tissue, and its ability to maintain considerable thickness and its impermeability to destructive chemical agents." Hollander looked upon the cellular layer as providing defense by immediately shedding the injured columnar cells and concomitantly reinforcing the secreted layer (mucus) with material of extra-high viscosity. He documented the rapidity with which this cellular layer regenerates itself and pointed it out as a crucial element in this hypothesis. Hollander commented that "it is curious that although Claude Bernard anticipated the importance of this dynamic quality of the surface layer in protecting the stomach against autodigestion, its role in this regard has almost completely been neglected during the intervening century." The facts suggested to him that ulcer etiology was more closely dependent upon predisposition to autodigestion than on secretion of excessive gastric juice, and he stressed the need for a shift of emphasis in research, holding this position long before any understanding of *H. pylori* or the role of NSAIDs in altering the mucosal barrier and in the causation of peptic ulcer disease.

Hollander proposed the gastric "mucus-mucosa" to be a virtually impenetrable barrier to the diffusion or absorption of HCl or to the exchange of H^+ for other ions across it. Therefore, all alterations in the concentration and composition of HCl collected from the gastric lumen resulted from neutralization and dilution. Support for Hollander's hypothesis came from Cope and co-workers (43, 44), who in 1943 demonstrated in dogs a strong gastric "epithelial barrier" to the diffusion of H^+ and other ions, as did Reitmeier et al. in humans, in 1957 (45). In 1963, Code and co-workers reported that the presence of acid within the gastric lumen led to a striking, almost complete, restriction of the movement of Na^+ ions across the membrane (46).

It remained unclear, however, whether this barrier to diffusion of ions (most notably H^+ and Na^+) was at the level of the surface epithelium or at the mucus layer, or both. Nevertheless, most authors began to refer to the epithelium as the site of restriction of ionic diffusion. This view arose in part from the apparent ease with which HCl secreted by the parietal cells found its way across the mucus layer and into the gastric lumen, as well as experiments which demonstrated the free movement of H^+ in both directions across refined films of gastric mucus *in vitro*. This objection to the mucus layer as being the protective barrier against acid in the lumen was met by Hollander with an educated speculation (42): "This seeming inconsistency in behavior might result from the formation of short-lived channels in the mucus layer. Immediately thereafter, the uncoagulated mucus surrounding the minute hole, by reason of its high surface tension, will flow over the opening and seal it."

Breaking the Barrier

This next stage in barrier research began in 1955 with a brief abstract (47) in which Hollander drew attention to Davenport's report that acid secretion by mouse stomachs *in vitro* was inhibited by the enzyme inhibitors iodoacetamide and N-ethyl maleimide (48). Hollander stated that "at Davenport's suggestion, we have attempted to confirm this effect *in vivo*." Hollander found that topical application of these substances to the mucosa, followed by parenteral histamine stimulation, resulted in a marked increase in volume rate of secretion without a drop in pH (49). Surprisingly, neither Hollander in this study (49), nor Davenport in his (48), considered the possibility that this finding might have resulted from a disruption of the mucous barrier, and that hydrochloric acid continued to be secreted by the parietal cells only to back-diffuse across this impaired barrier and be lost before it could be recovered for titration. This possible explanation may have been obscured by the fact that, in the absence of histamine, these enzyme inhibitors led to the output of significant volumes of viscous alkaline mucus secretion. Similarly, in 1952, when Janowitz, Colcher and Hollander concluded that secretion of HCl by canine gastric pouches in response to repeated injections of histamine had been markedly inhibited by acetazolamide (a new and powerful carbonic anhydrase inhibitor), they too ignored the possibility that acetazolamide might be causing a disruption of the barrier, with loss of secreted hydrogen ions by back-diffusion rather than by true inhibition at the parietal cell level (50). In support of their conclusion, Janowitz, Colcher and Hollander referred to a paper by Davies and Edelman (51), who studied tied tubes of frog mucosa and found "acid already secreted began to leak back through the mucosa" after application of carbonic anhydrase inhibitors. They ascribed this result to damaged parietal cells (51). Janowitz and Hollander also failed to make the connection and did not mention the possibility that the gastric mucosal barrier was being impaired by acetazolamide.

This oversight was corrected, quite by accident, in the fall of 1960. Mario Altamirano, a brilliant young physiologist from Santiago, Chile, who had established an international reputation with his studies on the permeability of the gastric mucosa, came to work with Hollander. He brought with him his ingenious lucite chamber device, in which a segment of gastric fundus with intact blood supply was mounted between two layers of lucite so that the mucosa formed the bottom of a cup. This so-called *vivo-vitro* preparation allowed for nearly quantitative instillation and collections, as well as continuous direct observation of the gastric mucosa itself (52). I borrowed Altamirano's chamber and in the course of a pilot experiment on the effects of acetazolamide on potassium in gastric secretion, I noted the sudden appearance of striking gross mucosal damage after intravenous acetazolamide when HCl was in the chamber in contact with the mucosa. This unexpected observation prompted a series of experiments designed to evaluate the degree to which mucosal damage might have contributed to the apparent inhibition of acid secretion following administration of this compound. Test solutions were placed in the chamber to control the acidity of the fluid bathing the mucosa, and acid secretion was stimulated by histamine. Administration of acetazolamide to preparations with high concentrations of HCl in contact with the mucosa resulted in prompt gross damage, with hemorrhage and edema. When the acidity of the chamber fluid was reduced by the addition of a buffer (glycine), the degree of damage and the degree of acid inhibition diminished proportionately to the reduction in acidity. The resulting paper (53) was the first to describe the consequences of impairment of the gastric mucosal barrier function leading to back-diffusion of H^+. It was also the first to point out that what appeared to be inhibition of stimulated acid secretion was in fact a consequence of H^+ loss by back-diffusion. When this paper was presented, Charles Code questioned the results, because the experiments had been done using a chambered gastric segment preparation, which in his view might have led to damage of the mucosa even though the blood supply was thought to be intact. He proposed that the experiment needed to be repeated in isolated canine pouches and emphasized that Janowitz, Colcher, and Hollander had not found any such damage or impairment of the barrier (50).

In 1962, Horace Davenport, chairman of the Department of Physiology at the University of Michigan, spent a sabbatical year at the Mayo Clinic with Dr. Code. At the Mayo Clinic, he held the title of visiting professor, but he asked Code (36) to "treat him as a post-doctoral fellow and assign a research project to him." Early in the fall of 1962, Hollander received a telephone call from Code and Davenport, asking his advice. Hollander beamed as he recounted to me the details of the long conversation: Code would assign Davenport a study on acid and sodium movement across the mucosa in canine gastric pouches damaged by eugenol, in accordance with Hollander's eugenol experiments. By Hollander's account, information was freely shared, and he was delighted at the prospect of these highly regarded physiologists starting a project so close to Hollander's heart, and so much derived from his ideas and previous work.

In 1981, at the time of his presentation of the Friedenwald Medal to Davenport, Code spoke (36) of the arrival of Davenport at Code's laboratory, and of the barrier research project: "The investigation, I thought, was one for which he was uniquely qualified. I had found a year or two earlier that when I washed out canine gastric pouches with an emulsion of eugenol, the active ingredient of the oil of cloves, the secretion of the pouch in response to histamine changed from hydrochloric acid to sodium chloride. Was the eugenol altering the product of the parietal cells, or was the hydrogen ion they secreted escaping after its formation?" The rest is history. To quote Code, "Davenport took off like a jackrabbit. . . . He had two papers published before I had ours written!"

In his early publication on the subject in 1964, Davenport and colleagues followed Hollander's lead, using eugenol to alter the barrier, and showed that eugenol damage did not alter acid secretion but rather that secreted hydrogen ions back-diffused across a damaged barrier more rapidly (37). Davenport's important and highly regarded body of work from 1962 through 1982 enlarged and enhanced our understanding of the gastric mucosal barrier. As part of his quest to locate the site of the barrier, he went on to publish many papers documenting the effects of a variety of barrier breakers. Davenport clearly can be credited with the reawakening of interest in the gastric mucosal barrier, for it was these many critical and concise reports, published in popular clinical journals, which caught the attention of the medical world. At the same time, the Mount Sinai group continued its own studies on the barrier. Multiple publications by Hollander, Altamirano, Werther, Chapman, Dycke, Rudick, Janowitz, Himal, Lindner, and Berkowitz *(vide infra)* followed.

Interest in the gastric mucosal barrier was not only reawakened: it flourished. In fact, it became an exciting subject for research and filled many a program at national meetings. By this time, however, Hollander was terminally ill. Although treated with respect, Hollander and his work were generally met with a polite indifference and at times went unrecognized. Even the eloquent article by Johnson (54) stated that "all of those papers, written by numerous physiologists, pharmacologists, gastroenterologists, surgeons, anatomists, and probably others as well, on acetic acid, bile acids, aspirin, and ethanol damage to the gastric mucosa were prompted by Davenport's original studies." When Davenport's paper (37) was published in *Gastroenterology*, its editor, Dr. Morton I. Grossman, wrote that it would revolutionize the physiology of the stomach and added, without references: "Substances which break the gastric mucosal barrier cause desquamation of cells which are quickly replaced."

The final paper on the gastric mucous barrier co-authored by Hollander and published in his lifetime was the definitive report of the effects of barrier disruption by acetazolamide (55). The apparent inhibition of acid secretion after acetazolamide was in fact shown to result from increased loss of secreted H^+ from the luminal fluid by back-diffusion. Even very prolonged contact (5 hours) of the mucosa with strong HCl (160 mEq per liter) never resulted in damage. This remarkable ability of the mucosa to maintain solutions of high acidity within the gastric lumen was abruptly lost after acetazolamide administration. H^+ losses accelerated over time, and the increase in H^+ penetration caused more mucosal damage. Furthermore, mucosal damage did not depend upon active HCl secretion *per se* and therefore was not due to the accumulation of alkali within oxyntic cells, as had previously been thought (51). Microscopic examination of the tissues did not show early damage to the oxyntic cells, but instead found it to be in the surface mucosal cells.

Davenport initially suggested that the increase in Na^+ gain and H^+ loss associated with impairment of the mucosal barrier resulted from an acceleration of the normally minimal equilibration of these ions across the membrane. Opposing this view, the Mount Sinai group showed that a large part of the increased Na^+ output from damaged mucosae was associated with net water movement into the lumen (55). In later publications, Davenport accepted these findings. The second Mount Sinai group of barrier investigators (working apart from Hollander), Lindner, Cohen, Dreiling and Janowitz, studied the effects of acetazolamide in humans and also agreed (56). Altamirano (57) confirmed the absence of a transport mechanism involving Na^+ for H^+ exchange across the gastric mucosa and concluded that both ions diffuse independently, for which he suggested the term "interdiffusion."

Hollander died in 1966. At this point, Davenport (58) still disagreed strongly with Hollander's two-component theory: "It should be noted that Hollander included the epithelial cells as half the barrier. . . although the layer of mucus is equivalent to a thin sheet of unstirred fluid, it provides little chemical protection for the mucosa; its chief function is lubrication. . . . Acid quickly diffuses through it to reach the apical border of the cells."

Thus, Davenport dismissed the mucus layer as nothing more than a lubricant. He gave no direct evidence to support this view, but referred to the work of others using refined mucus films. Davenport proposed that most of the barrier function of the mucosa was at the level of the apical membrane of the surface epithelial cells and at the tight intercellular junctions of the gastric mucosa. The luminal surface of the epithelial cell has no carrier for the ionic transport (as do the basolateral cell membranes) and the tight junctions appear to be much tighter than those found elsewhere in the GI tract. However, the mucus layer was later shown to possess a notable pH gradient from acidic at its luminal surface to neutral at the mucosal surface (59). This near-neutrality was maintained at the epithelial membrane surface by bicarbonate secretion into the mucus layer from the mucosa itself.

It was not long before Davenport began to retract his opposition to Hollander's views. In February 1968 (60), two years after Hollander's death, he published a subscript dedication: "This paper is dedicated to the memory of Franklin Hollander in gratitude for early encouragement and in appreciation of his contributions to the physiology of the gastric mucosal barrier." In this paper, Davenport wrote, "Although the exact locus and nature of the barrier are unknown, one component must be the plasma membrane of the mucosal cells, and another component may be the mucus layer at the tips of the epithelial cells." In addition, he credited Hollander's 1954 paper (43) with defining the two-component barrier. Davenport speculated that detergents might loosen the tight junctions and/or disrupt the plasma membrane of cells, and he cited evidence (61) that urea is capable of dissolving gastric mucus.

After Hollander

In the post-Hollander period, the Mount Sinai barrier investigators continued their studies.

Some are presented here as representative of that group.

Previous studies showing a "tight" barrier to H^+ and Na^+ had utilized *vivo-vitro* preparations (55) or isolated canine pouches, which consisted of oxyntic gland area only (62). Studies on the intact human stomach indicated a more rapid movement of hydrogen and sodium ions across the membrane than would have been anticipated from the canine studies, which employed oxyntic gland area only (63). Citing this disparity, as well as the known physiological relationship between antral acidification and the inhibition of gastric release, Walter Dyck, then a fellow in Gastroenterology at Mount Sinai, working with Werther, Rudick and Janowitz, studied separated canine pouches constructed from antrum or corpus (64). The antral mucosa absorbed more H^+ and put out greater amounts of Na^+ and K^+ than did the oxyntic mucosa. Dyck continued his work on the barrier and on other aspects of gastric pathophysiology during his fellowship and later as chief of the Gastroenterology Division and director of Research and Education at the Scott and White Clinic and Texas A and M University Health Science Center.

At this point, it had been established that the administration of acetazolamide, as well as topical chemical injury to the gastric mucosa, resulted in a loss of resistance of the mucosal barrier to acid absorption. Practically nothing was known about the nature and importance of this process in the diseased human stomach. Perhaps the hypoacidity as well as the ulcers in patients with gastric ulcer disease resulted from an altered barrier. Therefore, Chapman, Werther, and Janowitz studied the responses of the normal and abnormal human gastric mucosa to an instilled acid load (65). The patients with larger and more proximal ulcers were found to have a greater gastric permeability to H^+ and Na^+, as did patients with pernicious anemia.

Increased bile regurgitation into the stomach occurs in gastric ulcer disease (66–68) and the concentration of bile salts within the stomach returns to normal after the ulcers have healed. Davenport had shown that dog bile and sodium taurocholate caused an increased permeability of the gastric mucosa to H^+ in oxyntic-gland-area canine pouches (60); however, peptic ulcers of the stomach occur in pyloric-gland-area mucosa, not oxyntic. Werther and colleagues therefore studied the effects of human hepatic bile on electrolyte movements across the pyloric gland area in canine pouches and compared them with oxyntic gland area in the same dog (69). Their findings indicated that brief exposure to human bile in relatively low concentration markedly increased the net flux of Na^+, K^+, and H^+ across the pyloric-gland-area gastric mucosa. These results supported the hypothesis that at least part of the mucosal abnormality in gastric ulcer disease may reflect damage from increased back-diffusion of H^+ through a functional barrier which has been diminished by contact with bile. In the same issue of *Gastroenterology*, in 1970, Ivey and colleagues reported similar effects of bile salts on the gastric mucosa of human subjects (70).

Jack Rudick was appointed assistant professor of surgery at the Mount Sinai School of Medicine in 1966. Before he arrived at Mount Sinai, he had been a research associate at the University of Washington School of Medicine in Seattle. In 1968, he joined Werther, Dyck, Chapman and Janowitz in their studies on the barrier. Rudick's surgical skills, intellect and high energy added importantly to the work of this group, which found that atropine administration in both fundic and antral pouches in dogs resulted in an increased H^+ diffusion into the mucosa (71). They concluded that some of the apparent reduction in secretory rate after atropine was, in fact, the result of these H^+ losses. Other investigators did not agree (72), finding to the contrary that atropine did not affect the permeability of the gastric mucosa.

From the earliest observations on the gastric resistance to autodigestion, investigators had suggested that impairment of blood flow (especially localized) might be responsible for decreased resistance. The Mount Sinai group then validated aminopyrine clearance as a measure of mucosal blood flow, but aminopyrine itself was shown in this study to alter the permeability of both antral and fundic mucosa for H^+ and Na^+ (73, 74).

The Mount Sinai barrier group also reported that pentagastrin infusion tightened the barrier (75) and others agreed (76). Overholt, a student of Davenport, had previously attempted to estimate H^+ back-diffusion rates by utilizing glycine to trap secreted H^+ in the gastric lumen in human subjects (77). However, glycine had been shown to stimulate acid secretion (78), negating Overholt's results. Chapman, Werther, Rudick and Janowitz applied this glycine technique to patients with gastric ulcer, duodenal ulcer and gastric cancer and found increased permeability of the stomach to endogenous and exogenous H^+ ions in gastric ulcer disease and diminished permeability in duodenal ulcer disease (79). They corrected the problem of glycine augmentation of acid secretion by utilizing the glycine trap against a background of maximum acid output during full dose pentagastric infusion. Chapman was then a fellow in gastroenterology at Mount Sinai, later rising to associate clinical professor. He made important contributions to the work of the Mount Sinai gastric mucosal barrier study group and was lead author or co-author on seven papers relating to the gastric mucosal barrier.

Utilizing *vivo-vitro* chamber mounts of distal canine duodenum (80), the group then showed that the rate of movement of H^+, Na^+ and K^+ across duodenal mucosa was twice the rate for the antrum and 30–100 times that of the fundus of the stomach.

Werther and Horowitz clarified the controversial role of the gastric mucosal barrier to back-diffusion of H^+ in the pathogenesis of gastric ulcerations produced by restraint-stress in rats (81). Acid secretion did not decrease during restraint-stress, but there was a marked increase in hydrogen ion back-diffusion and loss across the gastric mucosa, which was clearly correlated with gross mucosal damage. They concluded that abnormal gastric mucosal permeability to hydrogen ions played an important role in restraint-stress-induced gastric ulceration.

Certain carcinogens, such as methylcholanthrene, are not absorbed by the normal stomach (82) and cause cancer experimentally only when they are surgically implanted in the gastric wall. Bile salts, which may reflux back into the stomach from the duodenum, promote absorption of such carcinogens by micelle formation. Horowitz and Werther showed that radiolabelled micelles of 3-methylcholanthrene, prepared *in vitro,* were absorbed by the gastric mucosa of the rat (83).

Some nitrosamines (N-methyl-N-nitro-N-nitrosoguanidine [MNNG]) are potent carcinogens site-specific for the stomach. Early inflammatory changes in the gastric mucosa occurred after administration of MNNG, followed by the occurrence of gastric cancer. Horowitz, Toth and Werther showed that the gastric mucosal barrier to hydrogen ions was markedly impaired after the administration of MNNG (84). Increased hydrogen back-diffusion was observed three hours after small doses of MNNG, both with carcinogenic, as well as with subcarcinogenic concentrations, so that barrier disruption by MNNG may play a role in gastric carcinogenesis by this agent.

The Mount Sinai group then reported (85) the effects of stress, aspirin and sodium taurocholate on the activity of MNNG in the stomach of the Buffalo rat, which is uniquely resistant to gastric carcinogenesis from any source, including MNNG. Adenocarcinomas and even greater numbers of gastric leiomyosarcomas were produced in these animals after barrier disruption by these agents. However, Buffalo rats receiving MNNG in the absence of restraint-stress, aspirin or taurocholate did not develop either gastric adenocarcinoma or leiomyosarcoma, so that at least part of the resistance of this unique strain to gastric cancer may be related to its mucosal barrier.

Mucus Revisited

The intense focus on gastric epithelium as a barrier gradually waned and was supplanted (in 1979) by a wave of interest in a phenomenon referred to as gastric "cytoprotection." This term related to the remarkable ability of gastric mucosa to resist gross injury by some extremely aggressive substances, such as boiling water, absolute alcohol, and concentrated corrosive solutions. Cytoprotection could be induced by prior exposure of the mucosa to a substance which would be irritating minimally injurious to the gastric lining. This gastric adaptation enabled the stomach to remain intact after exposure to these strongly aggressive agents. Since adaptive cytoprotection was blocked by inhibition of prostaglandin, it was suggested that exposure to a conditioning agent increased production of prostaglandin in the gastric mucosa, which in turn, in some mysterious way, was cytoprotective. However, there soon followed studies, utilizing both light and electron microscopy, which found that, in fact, the integrity of the surface epithelium was not maintained by this process. The term "cytoprotection" came into disfavor; however, the concept of mucosal protection by the effects of prostaglandins was documented and clarified. Increased thickness of the mucus layer provides most of the prostaglandin-induced cytoprotection (86–93). Recently, the mucus layer itself has been proposed as the site of the primary barrier (94).

If we accept the evidence that the mucus layer acts as a powerful diffusion barrier to hydrogen ions in the gastric lumen, how then does HCl secreted at the base of the gastric glands by the parietal cell traverse this mucus layer? Until 1990, the answer was obscure. Hollander had speculated on the possibility of short-lived channels but did not pursue this and presented no evidence. Fabry, working independently at Mount Sinai, provided the answer (95). Fabry described a process of viscous fingering, which is a hydrodynamic phenomenon by which fluids of low viscosity pass through fluids of high viscosity without mixing. In Fabry's model, pulses of hydrated HCl wind their way back through the mucus layer by means of short-lived channels or fingers. He proposed that surface tension makes the flat surface which the mucus layer presents to the lumen almost impermeable to the entry of hydrochloric acid. Driven by the secretory pressure of oxyntic cells, pulses of hydrochloric acid find their way through these channels in the mucus layer and into the lumen. After the secretory pressure drops, at the end of the pulse of acid secretion, the finger closes and disappears.

Lamont's group (96) confirmed Fabry's hypothesis. They documented viscous fingering patterns and showed the process to be dependent upon pH, so that "HCl secreted by the gastric gland can penetrate the mucus gel layer at the epithelial surface (pH 5–7) through these narrow fingers. Whereas, HCl in the lumen (pH 2) is prevented from diffusing back to the epithelium by the high viscosity of the gastric mucus gel on the lumenal side."

In the same year (1990), it was shown (97) that the mucus gel contained numerous phospholipids, and that its luminal surface was coated with a film of phospholipid. This surfactant layer accounts for the remarkably strong hydrophobic nature of the gastric luminal surface, which, in turn, provides protection against damaging agents. This phospholipid surfactant is a secretory component of the gastric surface mucosal cell.

Prostaglandin induces maintenance of the stomach's nonwettable surface properties protecting the underlying epithelium from aqueous acidic/proteolytic damaging agents in the lumen (98). This hydrophobic acid-resistant property of the gastric surface active phospholipid layer (SAPL) is rapidly attenuated by NSAIDs. As in humans, *Helicobacter* infection in mice is associated with a significant reduction in both gastric surface hydrophobicity and the phospholipid concentration of the oxyntic mucosa (99).

In a recent leading article in *Gut*, Hills emphasized that the stomach wall is strikingly hydrophobic (100). A droplet of water placed upon it "beads up as if on polyethylene." This hydrophobicity is largely eliminated by major "barrier breakers" such as bile salts and aspirin. A layer of hydrophobic surfactant transforms the hydrophilic mucoid layer into a surface so hydrophobic that the contact angle in many normal stomachs can exceed 90 degrees — that is, approaching that of polyethylene (93 degrees) or Teflon (108 degrees). The SAPL resides on the outermost layer of the gastric mucus (101). The source of this SAPL seems to be lamellar bodies found in parietal cells and mucus neck cells with some reported in chief cells.

The surfactant phospholipid is more permeable to lipids than to aqueous solutes. This finding fits well with the studies of discussed above in this paper. The Slomianys also found that stress ulcers are associated with a change in lipid profile of the gastric mucosa and that each of the known barrier-breakers displays some affinity for SAPL (102, 103). Bile salts form a chemical complex with SAPL, ethanol is a solvent for SAPL, while NSAIDs inhibit the production of prostaglandins controlling SAPL. Lichtenberger (99) has also shown that NSAIDs disrupt the surfactant phospholipid layer directly.

Recently, Hills (104), in a reply to a letter by Bernhard and Postle (105), agreed "on the major issue that surface active phospholipid (SAPL) protects the stomach wall from autodigestion by providing the gastric mucosal barrier to hydrated protons $H(H_20)_3{}^+$." However (104), "protons are far too polarizing to exist alone in an aqueous environment, the water of hydration being repelled by any hydrophobic domain."

Conclusion

Controversy over the locus of the gastric barrier has gradually faded and been replaced by disagreement. The importance of the mucus layer continues in its re-ascendancy; however, some physiologists continue to consider its major function to be lubrication (106). The importance of cytoprotection by prostaglandin-E_2 now receives considerable attention because of increasing concerns regarding NSAID-induced ulcers. However, these prostaglandins reduce gastric mucosal blood flow, which theoretically should be deleterious rather than helpful. Most would agree that enhanced mucus production, with thickening of the mucus layer, is the key to prostaglandin-induced cytoprotection. The apical cell membrane and the very tight gastric surface mucosal tight junctions are generally resistant to acid back-diffusion and may serve further to retard hydrogen ion back-diffusion. Some regard this membrane as the primary barrier. The layer of surfactant residing on the surface of the mucus layer is probably of great importance, but this is still being disputed. Most would agree that the pH gradient across the mucus layer exists and is important in the protective process. The problem with this latter hypothesis is that *H. pylori* may dwell close to the mucosal surface. *H. pylori* has very high levels of urease activity to make it an acid-tolerant neutrophil. This observation might lead one to the conclusion that the pH in the deeper mucus layer is, in fact, more acidic than microelectrode problems would indicate.

So what is the view from Mount Sinai at this time? We interpret the published evidence to show that the key protective mucosal barrier resides in the mucus layer itself, and that this derives from the nonwettable surfactant layer on its surface. The physico-chemical effect of the very high viscosity of the mucus layer and its ability to retain bicarbonate secreted by the epithelium with maintenance of a pH gradient is real and an important factor in protection. Our view of the barrier includes the surface epithelial cell layer for: (1) its easy desquamation, (2) its remarkably rapid regeneration, and (3) production of its bicarbonate and phospholipid surfactant. Last but not necessarily least is the resistance of the apical membrane of the surface epithelial cells to back-diffusion from ions.

All the work of a multitude of investigators, including the Mount Sinai group and Davenport, on the “barrier breakers” was important in understanding the nature of the barrier and the consequences of its disruption. However, since all these barrier breakers may function to disrupt the SAPL and mucus layer, as well as the surface epithelial cell at the apical membrane, the data do not give us critical information regarding the locus of the barrier. Evidence from the predilection of *H. pylori* to colonize the mucus layer close to the epithelium is circumstantial and indirect and cannot yet be considered definitive negation of the importance of the surface mucosal resistance to acid penetration. From the Mount Sinai point of view, the preferred area for *Helicobacter* colonization is the gastric antrum (pyloric gland area), because of the increased permeability of the antral mucus layer to acid as opposed to that of the nearly impenetrable surface of the oxyntic gland area mucus. From this viewpoint, sufficient acid passes through the antral mucus layer to satisfy *Helicobacter* and to reach the acid-sensitive neuroendocrine cells residing in the antral surface epithelium. We speculate that factors which increase the permeability of mucus overlying oxyntic gland areas lead to back-diffusion of enough acid to encourage cephalad extension of *Helicobacter* colonization into the gastric corpus and fundus.

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12

Gastrointestinal Hormones

Eugene Straus, M.D.

Abstract

Solomon A. Berson, M.D., the first Murray M. Rosenberg Professor and Chair of the Department of Medicine at Mount Sinai from 1968 until his death in 1972, and Rosalyn S. Yalow, Ph.D., 1977 Nobel Laureate in Medicine or Physiology and Solomon A. Berson Distinguished Professor-at-Large, brought meticulous quantitation and new vistas to all of clinical medicine and biomedical science through the application of their technique of radioimmunoassay. I was fortunate to know and work with them for many years. In 1972, while I was an NIH Fellow in gastroenterology at Mount Sinai, Dr. Berson suggested that I pursue my research in their laboratory at the Bronx Veterans Administration Hospital. Dr. Berson died one month after I began my research in the Bronx. Yalow and Berson had already discovered big gastrin (G-34), but much work with gastrin remained to be done. Challenging work with secretin, cholecystokinin, and a host of other gut peptides, would keep the Mount Sinai group at the forefront of this exciting field. **Key Words:** Radioimmunoassay, gastrointestinal hormones, regulatory peptides, gastrin, secretin, cholecystokinin.

> "Ros Yalow and Sol Berson were the Toscaninis of the field. . . . Most others were, if not organ-grinders, followers. . . ."
>
> Rolf Luft, M.D.
> Professor Emeritus of Endocrinology
> Karolinska Institutet, Stockholm
> Former Chairman, Nobel Committee (1)

Introduction

In 1902, conceptual and practical endocrinology began in London when Bayliss and Starling discovered secretin in the duodenal mucosa of a dog. They coined the term "hormone," suggesting that there were more chemical messengers to be found. Within a year, Edkins discovered gastrin in the mucosa of the gastric antrum. This was a major advance in medical knowledge. And nearly sixty years later, a discovery made by members of the Mount Sinai community would revolutionize endocrinology, as well as gastroenterology, hematology, virology, clinical pharmacology, oncology, and virtually every other area of medicine and biomedical science.

Berson and Yalow

The technique of radioimmunoassay (RIA) was introduced in 1959 by Solomon A. Berson, M.D., and Rosalyn S. Yalow, Ph.D. It is a method that can detect and measure extremely low concentrations of virtually any substance. They applied it first to the study of insulin, demonstrating that patients with Type 2 diabetes are resistant to its action. Subsequently, they and their younger colleagues studied many hormones and made the first RIA to detect an antigen, then known as Australian antigen, and now known to be a component of Hepatitis B virus. During their long association with Mount Sinai, their work was carried out in the Radioisotope Service of the Bronx Veterans Administration Hospital (VA).

Solomon Berson completed his residency training in internal medicine at the Bronx VA in 1950, and after a brief sojourn in private practice, he joined Rosalyn Yalow in the Radioisotope

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Service during the same year. Rosalyn had established the service in 1947. She was a nuclear physicist and had never taken a course in biology. At that time, Sol had scant background in research, but by 1968, he was appointed to serve as the Murray M. Rosenberg Professor and Chair of the Department of Medicine at the Mount Sinai School of Medicine. His death in 1972 ultimately cut short a brilliant career and eligibility for the Nobel Prize. In 1977, Dr. Yalow was awarded the Nobel Prize in Medicine or Physiology.

The history of gastrointestinal hormones at Mount Sinai is the story of Berson and Yalow, and the following is a brief summary (2). As this is a historical rather than a scientific review, the emphasis is on the major figures within the context of Mount Sinai. Technical reviews of the work involving gastrointestinal hormones, especially the contributions of members of the Mount Sinai community, can be found elsewhere (3, 4).

In 1950, the High Flux Isotope Reactor at Oak Ridge Tennessee was firing neutrons into the nuclei of atoms. It was often said that a physicist looking into the "swimming pool" reactor could see the blue glow of the neutrons streaming out and believe that the intellectual creations of Albert Einstein, Hans Bethe, and Enrico Fermi were the greatest works of art of the century. Nuclear physics had been Ros' first love. Fermi inspired her when she heard him speak in 1939, along with many others "hanging from the rafters in Room 301 of the Pupin Laboratory at Columbia University." However, with her new Ph.D., she joined IT&T, in 1945, working outside the field she loved. Then, when the soldiers returned from the war, she found herself replaced by a man. She took a tip from her husband, Aaron Yalow, who was working as a medical physicist at Montefiore Hospital, and went to work creating a nuclear medicine service at the Bronx VA. But Ros needed a bright physician to work with, and the Chief of Medicine at the VA, Dr. Bernard Straus, suggested Sol Berson. Berson had recently opened a practice on Long Island, which Straus regarded as a mistake. When the young nuclear physicist came looking for a research partner, Straus got Berson and Yalow together and, through his department, funded their early efforts.

Their work first grew from the circumstance of the availability of radioisotopes. When these two individuals, one with no background or knowledge of biology or medicine and the other with no knowledge of research or radioisotopes, joined force, something just "clicked." They worked with an intensity beyond passion, with little regard for themselves, and little regard for its effects upon those around them.

Radioimmunoassay

By 1955, Yalow and Berson were already well known and respected for their quantitative work in the areas of iodine and albumin metabolism. Then came their ability to measure peptide hormones, the proteins that act as chemical messengers and regulate body functions. Hormones like insulin, glucagon, growth hormone, parathormone, ACTH, gastrin, secretin, and cholecystokinin (CCK), some of which circulate in the blood at concentrations as low as 10^{-12} M, equivalent to the concentration of one teaspoon of sugar dissolved in a lake which is sixty-two miles long, sixty-two miles wide, and thirty feet deep. This was quite an accomplishment. And they were quick to realize that RIA could be applied to a vast array of endogenous and exogenous substances, because antigenicity, the ability to elicit an antibody response, as they had shown for insulin, was a far more general characteristic of molecules than had previously been thought. The commercial possibilities for RIA were enormous. In fact, RIAs have made fortunes for commercial laboratories and producers of assay kits.

"We never thought of patenting RIA," Yalow once told me, looking down her nose as though a dead fish had been placed before her. "Of course, others suggested this to us, but patents are about keeping things away from people for the purpose of making money. We wanted others to be able to use RIA. Now some people assume that I'm sorry, but I'm not. Anyway, we had no time for such nonsense."

Suddenly, physicians and researchers wanted to go meet and learn from the masters. And they came from everywhere: Guillemin, Rosselin and Assan from Paris; Isidori and Negri from Rome; Samols and Hartog from London; Thomopoulou from Athens; Devlin from Dublin; Gomez-Mont from Mexico; Scott from Auckland; McGarry, McKenzie, Colle and Schucher from Montreal; Beraud from Lausanne; Brauman from Brussels; Pimstone from Capetown; and Jadresec from Santiago de Chile, to mention just a few.

The guests would stay for a few days, or a week, or a month, and leave The Bronx with the secrets of RIA, with hands-on experience using the new method that was changing the world, and with the blessings of the masters. Many also took with them some of Berson and Yalow's precious antisera, the small volumes of guinea pig plasma containing specific antibody molecules, to enable them to begin to work quickly when they got home; for many it was the gift of a new direction in their work. All returned with stories of what it was like to be around Berson and Yalow, where concepts and approaches to problems flew between them and around the lab like tennis balls. "It was like bouncing ideas around," say many of the people who worked in the laboratory. It was the free exchange of ideas and the opportunity to participate which excited the visitors and fellows alike. Berson and Yalow were overpowering in the defense of their data when controversy arose, but they did not try to stifle the competition. They did not try to sell their antisera, and the suggestion that they patent their methods, as Yalow indicates, was met with frank derision. It truly can be said that they gave of their knowledge and materials and bade the scientific community to go forth and multiply. It is also true that they were intensely competitive, disinclined to collaborate with others, and frequently harsh and unforgiving in their criticism.

Among those who came to visit Berson and Yalow was the outstanding gastrointestinal physiologist and doyen of gastrointestinal hormones, Morton Grossman. Grossman was a good friend of Henry Janowitz and both had studied with Andrew Ivy, the discoverer of cholecystokinin. It was Mort Grossman who influenced Sol to enter the field of gastrointestinal hormones, and he introduced Ros and Sol to Rod Gregory, Michlos Bodansky and Victor Mutt, the researchers who purified gastrin, secretin, and cholecystokinin.

Gastrin

In 1970, Yalow and Berson reported their assay for gastrin and discovered "big gastrin," or G-34, the 34-amino-acid gastrin peptide (5). The major discovery that gastrin is found in tissues and blood in both 17- and 34-amino-acid forms, energized the gastrointestinal hormone research community. They brought both their technical expertise and their cutting edge understanding of hormone physiology to the study of gastrointestinal peptides, and they shared these, along with their gastrin antisera, with many individuals who would advance the field. Indeed, so influential was their finding of heterogeneous forms of plasma gastrin that it inspired some to see "micro-heterogeneity," or a plethora of innumerable gastrin forms. Nonetheless, their view that G-17 and G-34 are the predominant biologically active gastrin peptides mediating meal-stimulated acid secretion prevailed.

Since the major stimulus of gastric acid secretion is the ingestion of a meal, Berson and Yalow performed extensive studies of meal-stimulated gastrin release. Their findings uncovered a fundamental pathophysiologic mechanism associated with duodenal ulceration. Acidification of the antral portion of the stomach causes "feedback inhibition" of gastrin release. Since groups of duodenal ulcer patients have lower mean fasting gastric pH and higher rates of meal-stimulated acid secretion when compared with normals, they hypothesized that mean fasting plasma gastrin concentrations and integrated meal-stimulated gastrin release should be lower in groups of duodenal ulcer patients. Their observation that groups of duodenal ulcer patients had normal mean fasting gastrin levels and greater integrated meal-stimulated gastrin release indicated that, as a group, duodenal ulcer patients have relatively insensitive acid feedback inhibition of gastrin release (3). They further demonstrated that when acid feedback inhibition becomes grossly insensitive, a patient may display pathophysiology that mimics the autonomous hypergastrinemia of a gastrinoma (3, 6). They called this condition "non-tumorous hypergastrinemic hyperchlorhydria," admittedly a bit of a tongue twister, allowing others to rediscover this pathophysiology and apply the names "hypergastrinemia of antral origin" and "antral G-cell hyperplasia."

Subsequent work with gastrin demonstrated that the hyperchlorhydria resulting from extensive small bowel resection is caused by hypergastrinemia due to the absence of a gastrin release-inhibiting factor (7). In addition, the Mount Sinai group studied the molecular structure of gastrins from a variety of mammalian species, discovered gastrinomas in dogs and cats, traced gastrin-like peptides back to mollusks, and determined the distribution and metabolic fate of heterogeneous gastrin peptides (8–10).

Secretin and Cholecystokinin

With respect to the first hormone, secretin, the Mount Sinai group constructed the first successful assays (11, 12). Secretin had proven difficult to measure because the molecule, lacking a tyrosine, was difficult to label with radioactive iodine, and because it circulates in very low concentration. Nonetheless, methods of labeling the amino-terminal histidine and extraction from plasma using reverse-phase cartridges allowed demonstration of postprandial secretin release and hypersecretinemic states.

The Mount Sinai group played a central role in working out the technical problems in measuring cholecystokinin and in determining its complex heterogeneity and distribution in plasma, gut, and brain tissues (13 – 19). This group was the first to demonstrate that CCK is found in neurons of the cerebral cortex, that it is concentrated in synaptosomes, and that it is released by paradigms similar to those for nonpeptide neurotransmitters.

Conclusion

From the discovery of the first hormones, the regulatory peptides of the digestive system and the study of brain-gut peptides have been exciting and productive areas for the understanding of health and disease. We may take pride in the fact that members of the Mount Sinai community have contributed to this crucial area. In addition to Solomon Berson and Rosalyn Yalow, it is also worth mentioning Seymour Glick, Jesse Roth, John Walsh, and John Eng, each of whom has contributed greatly to this field both during and after their association with Mount Sinai. Those of us who have worked in the field are indebted to them all.

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Peptic Ulcer

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Abstract

Indigestion and heartburn have been described for thousands of years, but it was only in the 16th century that the disease peptic ulcer was established by autopsy. At first, only gastric ulcers were identified. In the 18th century, duodenal ulcers, most of which were fatal cases after perforation or hemorrhage, were seen. In the 19th century, when autopsy became a common, even routine, hospital procedure, uncomplicated acute and chronic ulcers were found and then correlated with symptoms. Thus, our current clinical understanding dates from the 1820s, by which time peptic ulcers were being reported in the U.S. It is unclear why gastric ulcers were not diagnosed at The Mount Sinai Hospital until 1873 and duodenal ulcers until 1885. However, after that time both conditions were diagnosed frequently, and they rapidly became common and were treated medically and surgically. **Key Words:** History, gastric ulcer, duodenal ulcer, U.S.

Gastric secretion and the mucosal barrier have been described in chapters 9–11, and surgical and medical treatments for peptic ulcer in chapters 10 and 14. This chapter explores the story of peptic ulcer through the centuries, in the U.S. and at The Mount Sinai Hospital.

Until recently, peptic ulcer was, as inflammatory bowel disease still is (see chapters 19 and 20), of increasing incidence, unknown etiopathology, and without rational cures. Our current understanding of the causative roles of acid and *Helicobacter pylori* and anti-inflammatory drugs in peptic ulcer does not explain its explosive increase in this century, so that historical research is necessary.

Upper abdominal discomfort and pain are described in ancient medical texts, and some patients who complained of a sour taste of bitter liquid may have had gastroesophageal reflux. Others may have had peptic ulcer, gall bladder disease or pancreatitis, but such retrospective diagnoses can be made only on autopsy reports, which were rare before the 16th century.

In the 15th century, Beneviene (1443–1502) described 111 cases, but only 15 of his autopsies have been published (1). One was a typical clinical case of pyloric stenosis (xxxvi): "The body was cut open for reasons of public welfare. It was found that the opening of his stomach had closed up and it had hardened down to the lowest part with the result that nothing could pass through to the organs beyond. . . ." However, Beneviene did not report an ulcer (and he was familiar with perforations of the small intestine), so that the stenosis may have been due to linitis plastica rather than to ulcer disease. Morgagni described a similar case, in which the history of vomiting dated back to soon after birth and then again from age 33 to 57. Prepyloric contraction was found; it may have represented adult "congenital" hypertrophic pyloric stenosis rather than post-ulcer stenosis (2). The first pyloric stenosis in association with a gastric ulcer (which had perforated terminally) was reported in 1727 (3), and the first hourglass stomach in 1732 (4).

Goldstein (5, 6) cites early descriptions of gastric ulcer in 1479 (7), 1519 (8) and 1581 (9). One of the first autopsy-proven pyloric peptic ulcers was published in 1586 by Donatus of Mantua. The patient was a 59-year-old man of bilious disposition, who died after four days of acute and persistent vomiting (10). When Cardinal Caesar Boronius died in 1607 after intractable nausea, the autopsy showed three ulcers in the mouth (cardia?) of the stomach (11).

The Bolognese painter Elisabetta Sirani died suddenly in 1665 (at age 27) after a few months of abdominal pain and one day of severe pain and collapse. The autopsy showed that she had a perforation of the stom-

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ach; two doctors diagnosed an inflammatory ulcer. However, two other doctors attributed the hole to a corrosive poison, and a maidservant was tried for murder but not convicted (12). Charles I's daughter, Henriette-Anne, died suddenly in 1670 (at age 26) after a day of abdominal pain and tenderness. The autopsy, performed to see if she had been poisoned, showed peritonitis and a small hole in the anterior wall of the middle of the stomach. However, the doctors had never heard of a peptic ulcer, let alone a perforation, and attributed the hole in the stomach to the knife of the dissector (12, 13). An early report (about 1600) of perforated gastric ulcer in a doctor's wife, age 18, indicated that she died after four days of abdominal pain, vomiting and peritonitis; Bauhin, in 1679, concluded that inflammation of the stomach led to a gastric ulcer which then ruptured (14).

The first known gastric hemorrhage was reported in 1704 (15); it was thought to be iatrogenic: "It is clear that the stomach ulcer caused the large quantity of blood which had come from many open blood vessels but the cause of the ulcer one suspects could be due to the violent medicaments given the patient by a physician of little experience." Morgagni (16) described duodenal erosions (but not ulcer) (XXIX.20) in 1737 as well as gastric erosions and ulcers (in 1735), one of which (XXIX.14) had a hole which Morgagni was certain was a perforation and not a dissector's incision.

In 1791 in Padua, Jacob Penada saw an alcoholic butcher of 35 with a four-week history of abdominal pain, worse in the patient's final 24 hours, with vomiting and collapse. Autopsy showed, and Penada illustrated, a perforated ulcer on the anterior wall of the duodenum (17). Although he did a literature search, Penada was unaware of a similar case in 1746 (18) or Sir George Baker's case of hematemesis and melena from an ulcer in the first part of the duodenum, reported in a footnote in the second edition (1772) of his 1767 lecture on lead colic (19).

The first classification of stomach diseases came in 1793 from Matthew Baillie (20), with clear descriptions of acute inflammation (arsenic), trichobezoar, ulcer, perforation, pyloric stenosis, and scirrhous and ulcerated cancer. In 1817, patients with perforated gastric ulcer were reported in Dublin by Crampton (21), and patients with perforated duodenal ulcer were reported in London by Travers, who also noted bleeding, stenosing and penetrating gastric ulcers (22). Sometimes, in retrospect, early reports of ulceration or perforation of the duodenum appear to have been tuberculous (23) or malignant (24). Identification of the anatomy and pathology of *ulcus simplex chronica* of the stomach is usually attributed to Cruveilhier (25), but in various editions (26), Abercrombie had already covered symptomatology, pathology and complications of ulceration, both in the duodenum and the stomach, and had reviewed the literature, mostly French.

Proof that chronic stomach ulcers could cause pain came when patients with recurring, years-long chronic stomach pains died of another disease, and ulcers were found at autopsy (27), in contrast to such diagnosis being made after a fatal complication of the ulcer. Nevertheless, ulcers found at autopsy could have been coincidental, rather than causing the symptoms, as is suggested by the later report of a patient who died of heart disease who had never had stomach pains, yet was found to have a chronic gastric ulcer (28). Of Rokitansky's 79 cases of perforated ulcer, only 6 were duodenal, with 16 prepyloric, 15 lesser curve, 20 posterior, 5 anterior; 1 in the cardia and 16 multiple (29, 30).

Incidence of Gastric and Duodenal Ulcer

In 1857, Brinton (31) found a gastric ulcer or scar in 5% of all autopsies, whereas Perry and Shaw (32) found 70 duodenal ulcers in 17,652 routine postmortems (that is, 0.4%) at Guy's Hospital, London, 1826–1892. Of these 70 cases, 9 were fatal by hemorrhage, 8 by perforation, and 3 as the result of cicatricial narrowing either of the bowel or of the common bile duct (32). In the other 50 cases, the ulcer was found at routine autopsy.

Perry and Shaw (32) added to their own 70 cases another 81 from the British journals and hospital reports, to make a total 151 patients, 60 of whose complications included 32 with hemorrhage, 56 with perforation and 33 with obstruction. However, 91 of the 151 had been free of abdominal symptoms until complications or their death from other causes. Duodenal ulcer became more noteworthy after its convincing association in 1842 with burns, although Curling (33) was careful to point out that the association between burns and inflammation, congestion and ulceration of the intestine (but not specifically the duodenum) had previously been noted by Dupuytren (34) (and even earlier, in 1823 [35]). Moreover, three of John Hunter's six autopsies from 1755–1781 on patients with gastroduodenal erosions/ulcers (36) were acute, related to one patient with fever and two with fractured skull. A patient with gastric ulcers after burns was reported by Swan in 1823 (37), and one with both duodenal and gastric ulcers by Cooper in 1839 (38). Meanwhile, the 1st (1882) and 2nd (1892) series of the Index-Catalogue of the Library of the Surgeon-General both have three columns of citations, from 16 countries, of papers on duodenal ulcer (and 23 and 64 columns respectively on gastric ulcer), with 16 monographs on duodenal and 35 on gastric ulcers, mostly in German and French.

Peptic Ulcer in the U.S.

Goldstein (5) claimed that the earliest reference to a peptic ulcer in an American patient was in 1761 by Morgagni (16). However, Goldstein was relying on

Alexander's English translation of 1769 (16), where the "in an American" is a mistranslation of "in Marsupiali Americano," which was the opossum dissected by Tyson in 1698 (39); Morgagni had read of the dissection in a Latin report from that year (40) rather than in the English original (39). Nevertheless, Tyson was not only the first to report an animal with a (perforated) peptic ulcer, but he claimed to have seen three such perforated ulcers in patients, and in one he claimed he had foretold the diagnosis "before the *Patient's* Death" (41).

The first three Surgeon General's Catalogues list 64 reports on 101 patients with duodenal ulcer in the U.S. in the 19th century. It is interesting to compare their timing with the 68 reports from the U.K. on 211 patients, including the 201 cases collected by Perry and Shaw (32) (Table). It seems clear that, as in Britain, duodenal ulcer was increasingly reported in the U.S. from the middle of the 19th century, especially from the 1870s, after the diagnosis was made from fatal cases of hemorrhage and perforation.

With the advances in operative and anesthetic techniques, surgeons were able to perform laparotomy for gastric ulcer, at first for emergencies and then electively. Series of such operations with reviews of the literature were reported in the early 1900s, both from Leeds (42, 43) and the U.S. (44), and especially from the Mayo Clinic (45–47) which performed 2263 ulcer operations between 1906 and 1915 (48).

Peptic Ulcer at Mount Sinai

"Gastric Ulcer" appears in *Mount Sinai Annual Reports* continually from 1873, at first with about one case per year and increasing to five cases annually in the 1890s, but only with cases of perforation, stenosis or hemorrhage. Then, according to the 1901 report of the 1st surgical division, Fannie S., a woman of 18, was admitted with epigastric pain and massive hematemesis, which continued for six days while she was in a bed in a medical ward. When she was exsanguinated, the internist requested the surgeons to perform laparotomy, which showed a large prepyloric lesser curve ulcer with a large vessel pulsating underneath its floor. She died 14 hours later. "Epicrisis — A fundamental rule of medicine is the checking of dangerous hemorrhage. There is no reason why a dangerous hemorrhage issuing from the stomach should form an exception to this rule. It seems that in this case more prompt interference might have checked the hemorrhage and eliminated the ulcer."

TABLE

Reports of Duodenal Ulcer in the 19th Century in the U.K. and U.S.

Decade	U.K.		U.S.	
	Reports	Patients	Reports	Patients
1810–1819	2	2		
1820–1829	2	6		
1830–1839	1	10	1	1
1840–1849	9	31	2	3
1850–1859	7	20	6	9
1860–1869	7	23	5	8
1870–1879	11	42	9	10
1880–1889	9	26	13	13
1890–1899	20	51	28	57
Total — 19th century	68	211	64	101

Sources:

U.K. and U.S. reports Surgeon General's Catalogues of 1882; 3:953–955, 1899; 4:557–559 and 1923; 4:782–796.

U.K. patients: Perry & Shaw 1893–1894 (32):70 cases from Guy's Hospital, London, 1826–1892 and 131 reports published between 1810 and 1892, for a total of 201. The Surgeon General's Catalogues provided 10 more cases.

Duodenal Ulcer at The Mount Sinai Hospital

It remains unclear why duodenal ulcer was so rare at Mount Sinai until the early 1900s; possibly routine autopsies were not feasible on Jewish patients, but hemorrhage, perforation and stenosis would have been easily diagnosed while they were alive. "Duodenal Ulcer" appears in *Mount Sinai Annual Reports* as single cases in 1885 and 1893, with perforation in 1901 and 1902, as stenosis in 1903, as 5 cases of perforation in 1901 and 1902, as stenosing in 1903 and 1905, and as 5 cases of perforation in 1906, after which time the number of admissions increased each year. The 1901 admission was for right iliac fossa pain with pus found at incision at that site. However, no further exploration was done, and the autopsy showed perforations both in the duodenum 8 cm from the pylorus and in the ascending colon.

Admissions for peptic ulcer soon increased so rapidly that, in the two years 1903 and 1904, Berg's services operated on 1 duodenal ulcer and 18 gastric ulcers, of which 6 were uncomplicated, 3 each were after hemorrhage and perforation, 6 were with stenosis, and 1 was a recurrence after gastrojejunostomy (49). Such recurrences at Mount Sinai of peptic ulcer at the stoma after the then-standard operation led to the change in practice at Mount Sinai in the 1920s and 1930s from gastroenterostomy to partial gastrectomy (see chapter 10).

The commonest gastroenterological case at Mount Sinai in the19th century was calculated to be gastralgia, meaning upper abdominal symptoms (see chapter 7). In today's clinics and private offices, these symptoms are similarly frequent. Some patients are diagnosed after tests as having peptic ulcer, gastro-esophageal reflux, gall bladder ulcer or pancreatitis, but most are categorized with the neutral and unhelpful term "non-ulcer dyspepsia," because it is still unclear whether there is a disturbance of function of the stomach (dyskinesia) or a functional disturbance of the patient. In 1882, the *British Medical Journal* claimed that the cause of dyspepsia in the U.S. was ice water (50): "The prevalent dyspepsia from which Americans suffer so much, and which is so apt to undermine the strength of the men and the bloom of the women of America, is in a large measure due, we believe, to the universal habit of drinking large quantities of ice-water. This essentially transatlantic habit has long been a speciality of which our American friends and travelers seem to be proud, complaining that they find the purest water in England undrinkable, from the difficulty of getting water to drink with lumps of ice floating about in it. Nothing can be more destructive to the utility of the process of digestion than this habit."

However, dyspepsia was and still is common in the U.K., where ice water is still uncommon, and the problem remains unsolved. The treatment of dyspepsia and peptic ulcer is discussed in the following chapter.

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14

Treatments of Peptic Ulcer

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Abstract

From the late 19th century, Mount Sinai gastroenterologists declared their scepticism of the efficacy of all recommended treatments of peptic ulcer, and looked forward to trials which could distinguish between sequence and consequence, between association and causation. The rationale of all the early studies was to reduce gastric acidity, but it soon became clear that any neutralization by single doses of antacids was brief and ineffective. Winkelstein's demonstration that patients with duodenal ulcer had higher acidities not only before and after meals but also through the night hours led him to introduce a new treatment, the alkalinized intragastric milk drip together with atropine. One of the earliest controlled clinical trials at Mount Sinai compared different antacid regimes and showed that pH values above 3.5 were achieved in only about half of the patients on the various drips. When the new anticholinergic drugs were developed in the 1950s, they were found to produce sustained hypoacidity and were tried as maintenance treatment, as an alternative to acid-lowering operations. The third Mount Sinai approach was to "attack the machinery of the acid-producing cell itself" by an inhibitor of the enzyme producing hydrogen ions. In 1939, this enzyme had been thought to be carbonic anhydrase, but when Janowitz and Hollander tested its inhibitor, acetazolamide, and showed marked but very brief acid inhibition, they concluded that its action was too brief to be therapeutically useful. The problem was to be solved decades later by H_2 receptor blockers from Britain and H^+K^+ATPase inhibitors from Sweden. **Key Words:** Acid inhibitors, antacids, anticholinergic drugs, acetazolamide, controlled trials.

In the last hundred years, Mount Sinai gastroenterologists have swung between critical caution and uncritical enthusiasm in their use of the countless new remedies periodically made available to the profession. Manges was particularly scathing about the use of ferments such as pepsin, rennet, papain, papayatin, papoid, caroid, bromelin, ptyalin, diastase, maltine, and taka-diastase (1): "The prevailing idea is that the ferments exist in the body; therefore their administration, even if accomplishing no good, will surely do no harm. A most pernicious doctrine! . . . the sphere of usefulness of the ferments is a limited one, and although this fact is emphasized in every textbook on the diseases of the stomach, yet on account of the glamour which still surrounds the ferments, it is not practically accepted by the profession at large."

In 1900, Manges reviewed "the unanimity which prevails among medical writers on the subject of the diet of typhoid fever," which then had to be liquid and bland. Manges was skeptical, and noted that a series of patients in Leeds, England had seemed to fare no worse when fed generously. More important, Manges then (perhaps for the first time at The Mount Sinai Hospital) cited a controlled clinical trial, in Russia, where in 1896–1897, 80 patients with typhoid admitted to one ward were well fed and, based on 12 criteria, did as well as 74 other patients who were admitted at the same time to another ward and kept on a liquid diet (2).

Although of limited value in diagnosis, the test meal was often used to assess therapy. In the early years of this century, dilute hydrochloric acid was widely used in the treatment of dyspepsia, but Crohn showed that conventional doses of HCl given infrequently had minimal effects on intragastric acidity; only large doses every 15–30 minutes were effective chemically, but in no way stimulated the mucosa (3). Similarly, Crohn confirmed that antacid neutralization depended on the

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cation (sodium, magnesium) and anion (bicarbonate, oxide), the dose and the frequency of the dosage, and was followed by rebound hyperacidity (4). Crohn also studied olive oil, belladonna, bismuth and atropine, but again without any novel findings (4).

Diets were the standard treatment for ulcer for most of the 20th century, and Crohn and Reiss (5) investigated their clinical efficacy, together with their acid-lowering effect. For the first time in Mount Sinai gastroenterology, critical biometrical distinctions were drawn between sequence and consequence, and between association and causation:

> Medical treatment resulted in a net reduction of acidity in 13 out of a series of 34 cases (38 per cent). If we wish to consider only those cases with definite hyperchlorhydria, omitting all cases with iso- or hyposecretory curves, the percentage of net lowering of acidity is still lower (30.3 per cent). Of these 13 cases chemically benefited, 12 or 92 per cent, were discharged free of symptoms. Loose reasoning might lead one to see a relationship of cause and effect in these figures. But if we analyze those cases in which treatment failed to invoke chemical relief, and these comprise the larger proportion, we find, despite this fact, clinical relief in 13, or 62 per cent of them. . . .
>
> We can draw . . . inferences from these figures. . . . Only a small percentage of ulcer cases react to medical treatment by showing a reduction of acid produced during digestion (38 per cent) . . . clinical improvement can take place independently of whether the hyperacidity is relieved or whether the case remains acid-fast. . . . Medical treatment, consisting of restricted diet and rest in bed, causes the cessation of hypersecretion in 45 per cent of the cases, a fair proportion; clinical improvement takes place as often in cases with persistent hypersecretion as in those relieved of their excessive flow of gastric juice, and is apparently not dependent upon it.

In 1929, Crohn studied for the first time a proprietary antacid, colloidal aluminum hydroxide "Alusol" (Wander) and concluded that it:

> . . . seems to be the more desirable of the neutral nonabsorbable antacid salts in so far as it is an efficient agent in reducing gastric acidity to a point where symptoms are relieved but gastric digestion allowed to continue. It hastens gastric emptying; it is nontoxic and devoid of deleterious by-effects. It is clinically applicable in cases of gastric secretory disturbances characterized by hyperacidity and can be used in ulcer cases in moderate dosage over prolonged periods without the anxiety of producing or the production of alkalosis or the toxic symptoms such as may be due to the absorption of soluble alkaline salts. (6)

Winkelstein, Crohn's successor as chief of the gastroenterology clinic at The Mount Sinai Hospital, introduced several new treatments for peptic ulcer. Atropine was known to reduce gastric acidity for up to two hours after a single dose. However, when Winkelstein (7) studied 40 patients whose free acidity had been reduced after partial gastrectomy from 50 – 80 mmol/L down to 15 – 34 mmol/L, atropine immediately reduced acidity to zero for more than two hours. He concluded that with the removal of the second (chemical) gastric phase of acid achieved by the partial gastrectomy, any persisting acid secretion must be vagally driven and potentially suppressible either by a vagotomy (see above) or by atropine (7). It was only twenty years later that he pursued this antimuscarinic approach, because meanwhile he had devised a new therapy.

Winkelstein knew that patients with duodenal ulcer had higher-than-normal acidity basally, postprandially and after sham or psychic feeding (8). He then devised a new (for the U.S.) test measuring acidity every two hours from 7 PM to 7 AM and found that patients with duodenal ulcer also had high nocturnal acidity (8, 9). Measurement of acidity throughout the night, on waking and after a meal, was an important advance in testing gastric secretion, which testing needed only to be extended to hourly measurement of pH throughout the 24 hours. This was not attempted until twenty years later by James and Pickering (10) and is still one of the gold standard tests for assessing the effects of acid-lowering diets, drugs and operations (11).

Winkelstein's Milk Drip

Winkelstein therefore suggested that the standard Sippy diet with cream and milk hourly for 12 hours daily, alkalies and evening aspiration could not cope with nocturnal acidification. In 1932, therefore, Winkelstein (11) dripped through an indwelling Rehfuss tube 3 quarts of milk and 15 g of $NaHCO_3$/day, which he calculated would theoretically neutralize 9 quarts of N/10 HCl. This novel alkanized milk drip did markedly decrease or even abolish free acidity at night: "To prevent psychic secretion, and this a point of considerable importance, food should not be seen nor discussed" (8). The treatment was given for 3 weeks together with atropine 3 or 4 times a day. The tube was then removed during the day while the patients had a Sippy regime, but the night alkaline milk drip was given as well for a further week. Symptomatic improvement occurred in hours with excellent sleep, and radiological healing of most ulcers (duodenal, gastric or jejunal) was achieved in 4 weeks, after which the patients could leave the hospital and it was feasible for them to resume the nightly drip at home if symptoms recurred.

Winkelstein's milk drip was widely used (and indeed by the author until the late 1950s) until effective acid inhibitors became available. Aluminum hydroxide, used as an antacid since 1922 and tested by Crohn in 1929 (6), was tried as an alternative to sodium bicarbonate so that Mount Sinai could then compare the biochemical effects (in one of its first controlled trials [12]). This scientific advance was almost certainly due to the arrival of Franklin Hollander in 1936 to direct the gastroenterology research laboratories, because the acidity measurements were now presented as pH and the results presented as mean pH, range and n (number of observations). The arithmetical mean nocturnal pH was calculated (deliberately and reasonably disregarding its logarithmic nature) to be and was 1.5, raised to satisfactory pH 4 by milk-bicarbonate, and aluminum phosphate or hydroxide with or without milk. However, calculations of the frequency distributions of individual pH values suggested that "no free acid, pH = 3.5–9.0, mEq/L < 1" was achieved in only about half of the patients on the various drips.

By 1945, Winkelsein (13) could report on 13 years' experience with the drip, which was now given through a soft latex tube rather than the semirigid Levin tube: "most of these patients are 'tube broken' having had various gastric analyses performed upon them, so that they do not find the method drastic or difficult." However, only 22 of 60 ulcer patients refractory to Sippy therapy responded to the milk drip. Nevertheless, the Mount Sinai group made a motion picture (14). The final development of the alkaline milk drip was to omit both alkali and milk and instead use a high-calorie, high-protein, high-neutralizing powder (15), which Winkelstein (16) claimed produced a favorable response on 35 of 40 private patients who were refractory to conventional ulcer therapy including anticholinergic drugs.

Winkelstein, throughout his long career, held that "the pathologic physiology of peptic ulcer is mediated through the dorsal vagi and nerves" (17) and he therefore encouraged both the addition of vagotomy to gastroenterostomy and partial gastrectomy as well as the nocturnal alkaline milk drip, while awaiting the marketing of a "medical vagotomy." That Winkelstein believed the precipitating cause of vagal hyperactivity was "an emotional psychogenic disturbance" will be discussed separately.

Anticholinergics

Winkelstein studied several of the new anticholinergics developed in the 1950s. In uncontrolled studies with methantheline bromide and despite minimal inhibition of basal and nocturnal postprandial or insulin-stimulated acidity "in an experience of 25 years with large numbers of ulcer patients, I have not encountered a drug which provides such excellent clinical results in such a large percentage of cases" (17). However, oxyphencyclimine (18) markedly inhibited the volume and acidity (by pH paper) of morning gastric juice residue 11 hours after 20 mg given at 9 PM, and similarly for juice volume three hours after 20 mg given with breakfast. All 96 patients had dry mouth but only 4 had to stop because of other side effects. Symptomatic response was good, encouraging Winkelstein for the first time to use the drug as maintenance treatment for a year or more. A third new anticholinergic, endobenzyline bromide, also gave favorable acid-reducing and clinical results (19).

Winkelstein was receptive to any novel rational therapy for peptic ulcer, such as increasing mucus secretion. Hollander had shown eugenol to be an effective mucigogue (20), so this compound was given to 14 patients, with the usual mixed response (21). Presumably because of the scientific background of Hollander, this was the only one of Winkelstein's papers on ulcer therapy which included conclusions such as "no correlation was found between clinical response and laboratory findings (x-ray and acidity curves). Because of this, and also because of the demonstrated lack of reliability of the patients' statements, we were unable to report any unequivocal beneficial effect of eugenol therapy . . ." (21). Another rational therapy which proved unsuccessful was physically induced pyrexia (22).

Enzyme Inhibitors

Hollander and Janowitz (23) categorized three mechanisms for reducing gastric acid in the treatment of peptic ulcer. The first, neutralizing acid already secreted into the lumen by antacids, had been studied at Mount Sinai (see above). The second, blockers of acetylcholine, had long been available in their natural forms of belladonna and atropine. New anticholinergics were synthesized in the 1940s and became available both for studies of animal and human gastric secretion and for treatment of peptic ulcer. Some of these drugs were tested at Mount Sinai (see above). However, homatropine, methscopolamine, methantheline, propantheline, oxyphenonium, penthienate, diphemanil, mepiperphenidol and dibutoline were not major clinical advances, because reductions of gastric acidity were slight unless dosage was so large as to cause adverse effects in other parts of the body, especially the eye, the bladder and the bowel.

Thus, a third approach was conceived (23): "The search for an ideal therapeutic agent would be to attack the machinery of the acid-producing cell itself." The compound they tested was acetazolamide, one of the potent inhibitors of carbonic anhydrase, the enzyme which catalyzes the hydration of carbon dioxide. In 1939, Davenport (24) showed that this zinc-containing enzyme was most concentrated in acid-secreting mucosa, and was correlated in cat and rat with the density of parietal cells. He suggested that it hydrated carbon dioxide to carbonic acid, which was ionized to hydrogen ions to be secreted into the lumen, and to bicarbonate ion to pass into the bloodstream.

$$CO_2 + H_2O \rightarrow H_2CO_3 \rightarrow H^+ + HCO_3^-$$

Davenport therefore suggested that carbonic anhydrase might be an essential agent for acid formation, and if it was, then an inhibitor of this enzyme would inhibit gastric acid secretion. Unfortunately, the early inhibitors such as sulfanilamide failed to inhibit gastric acid, and in 1946 Davenport retracted his theory (25). However, when newer inhibitors of carbonic anhydrase became available, the Mount Sinai group tested acetazolamide first in the dog (26) and then in man (27, 28).

In dogs with Heidenhain pouches, acetazolamide given intravenously in bolus doses of 5 – 120 mg/kg led after 20 – 80 min to inhibition of histamine-stimulated acid output lasting 3 – 6 hours, and with doses of 20 – 60 mg/kg, the reduction in acid ranged from 70 – 97% with no obvious side effects (26). Similar studies in humans in whom acetazolamide 35 – 154 mg/kg was infused intravenously over 1 to 8 hours showed profound and dose-related inhibition of 4 – 100% of histamine-stimulated gastric acid. A dose of 100 mg/kg produced 97% inhibition of basal acid output. With doses above 114 mg/kg, some subjects became breathless and anxious, and noted tingling of the extremities (27). Given orally, acetazolamide 30 mg/kg was ineffective, and while doses of 45 – 79 mg/kg did profoundly inhibit gastric acid, the effect lasted only one hour (28). Thus, while these studies did show a convincing role of carbonic anhydrase in catalyzing the removal and extrusion into the bloodstream of bicarbonate released by the secretion of HCl into the lumen, the drug, given orally, produced too short an inhibition for therapeutic usefulness when taken in tolerable doses (29).

Nevertheless, Hollander, in this innovative attempt at acid-lowering ulcer healing by inhibition of a specific enzyme inside the parietal cell, was prescient in his prophecy:

> We have serious hope that, within the next few years, there will be available to clinicians some chemical substance which blocks an enzyme which is more or less specific for the parietal cell — perhaps an enzyme which operates within the wall of the intracellular canaliculus, where we believe the hydrogen ion is separated to form hydrochloric acid. When this happy day comes, I think that duodenal ulcer will, in great measure, be removed from the category of surgical disease and became one which responds very early, very simply to medical therapy. (30)

However, the new inhibitors were not to come from The Mount Sinai Hospital or even from the U.S.; they came from Britain as H2 receptor blockers (cimetidine, ranitidine) and from Sweden as H^+K^+ATPase inhibitors (omeprazole). Thus, peptic ulcer was "removed from the category of surgical disease" by powerful new acid inhibitors even before these were superseded by therapy eradicating *Helicobacter pylori.*

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The Pancreas

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Abstract

Pancreatic secretion was first studied at The Mount Sinai Hospital by Crohn in 1912, but measurements of pancreatic enzymes in duodenal aspirate or feces were found unhelpful in diagnosis. Such pancreatic tests fell into disuse because of advances in radiology of the biliary tree in the 1920s. Once extracts of secretin and cholecystokinin-pancreozymin became available from Sweden in the 1930s, it became possible for the biochemist Franklin Hollander and the surgeon David Dreiling to develop pancreatic secretion tests into practical procedures for the diagnosis of benign and malignant diseases of the pancreas and biliary tree, and produce physiological studies of the mechanisms of ion transport. With more purified hormones, it became possible to measure maximum (alkaline) bicarbonate output of the pancreas analogous to the maximal acid response of the stomach to an augmented histamine test, and to determine whether patients with duodenal ulcer had decreased neutralization of gastric acid in the duodenum. Clinical studies were also directed to the pathophysiology of acute relapsing and chronic pancreatitis and carcinoma. However, advances in imaging and endoscopy have now shifted the thrust of pancreatology. **Key Words:** Pancreatic secretion, secretin, cholecystokinin-pancreozymin, pancreatitis, pancreatic carcinoma.

AS WITH THE STOMACH, there was close collaboration between the departments of medicine and surgery at The Mount Sinai Hospital in their studies of pancreatic physiology and disease.

Pancreatic Secretion

Crohn's chief, Dr. Julius Rudisch, was a friend of Dr. Max Einhorn (1862–1953) of the German (later Lenox Hill) Hospital, an early specialist in gastroenterology (1). Einhorn was one of the first to investigate the duodenal juices, and on a visit to The Mount Sinai Hospital presented two of his inventions, a duodenal bucket on a string and the flexible duodenal rubber tube, to Dr. Rudisch, who passed them on to Crohn because, according to Crohn (2), Rudisch was interested only in diabetes and not in gastroenterology. However, Rudisch certainly was interested in hepatogastroenterology and wrote on acute yellow atrophy of the liver (3). Moreover, in Crohn's own memoirs (4), The Mount Sinai Hospital attending in the anecdote is not Rudisch but Dr. Nathan Brill (who had written on primary carcinoma of the duodenum [5]). In 1912 Crohn, with the help of Dr. Bookman, the hospital biochemist, began his secretory studies.

> In order for me to study the diseases of the pancreas, it was important first to establish the norm. To put ward patients through the test, which is uncomfortable for even healthy persons, seemed an injustice. Who was more normal and more accessible than myself? Night after night, at bedtime, I would swallow that 36-inch long rubber catheter, drink a glass of milk to stimulate pancreatic secretion and go to sleep. In the morning I would aspirate the pancreatic secretions and the bile from my duodenum. The tube constituted no great discomfort or inconvenience and on every afternoon the secretions would be tested and the normal pancreatic enzymes evaluated at the laboratory. (4)

Statistics and biometry were not then used in clinical measurements. Crohn determined the

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normal ranges for the various constituents of the duodenal aspirate from samples of aspirate obtained 2$^1/_2$ hours after 8 ounces of milk which he drank at 6:30 AM. Samples were analyzed for amylase, lipase, and alkali protease in both duodenal aspirate and feces. Values were also obtained from patients with gallstones, pancreatitis and carcinoma, cirrhosis and diabetes (6). He was able to show the presence of normal pancreatic enzymes and the absence of bile in a 10-week-old infant in whom the bile ducts were absent (7).

Crohn tried to diagnose tumors involving the terminal bile and pancreatic ducts (8) and to distinguish between different causes of jaundice, such as cholecystitis and lithiasis, catarrhal jaundice and impacted common bile duct stones, and between benign and malignant strictures of the biliary system, pancreatitis, carcinoma of the pancreas, and liver cirrhosis (9, 10).

In this series of papers (6 – 10), Crohn always reviewed the literature (usually including the many tests devised by Einhorn) and disclaimed any fundamental novelty in his studies, or in his assessment of duodenal lavage with magnesium sulfate (11) or his experimental studies on gall bladder physiology at Cornell (12).

The Lyon test continued in use at The Mount Sinai Hospital at least until 1923 (13): "Since gall bladder disease, with its protean clinical manifestations, is a frequent cause of intra-abdominal symptoms (second only to disease of the appendix), this test should be included as . . . routine in the study of gastro-intestinal cases."

The Department of Physiologic Chemistry at The Mount Sinai Hospital continued to improve the assays for rennet and other pancreatic enzymes (14 – 16) and also performed the first quantitative measurements of the enzymes in juice draining from a pancreatic fistula (17). Pancreatic tests then fell into disuse, partly because they added little to clinical diagnosis, but mostly because of advances in radiology of the biliary tree in the 1920s.

Pancreatic Secretion Tests

Soon after Hollander came to Mount Sinai to direct the Gastroenterology Research Laboratory, Einar Hammarsten, professor of chemistry at the Karolinska Institute, Stockholm, came to give the 1938 Janeway Lecture on "The Secretin of Bayliss and Starling" (18). In it, he reviewed the work in his department to purify and crystallize this hormone and to prove that it was different from cholecystokinin and incretin. In this lecture, he referred to reports by Agren and Lagerlöf, and Agren, Lagerlöf and Berglund, and Lagerlöf, in which this secretin was used to test pancreatic secretion, using a double tube to aspirate gastric and duodenal juice separately over 60 minutes, and measuring volume, bicarbonate, diastase, trypsin and lipase.

It was this Stockholm test that Diamond (19) introduced in the United States and which Hollander's group then used extensively both in dog and man for more than 30 years. In July 1946, Dr. David Dreiling succeeded Dr. Henry Doubilet as the Dr. Ralph Colp Fellow in Experimental Surgery. At the time of Dr. Dreiling's graduation from the house staff, Dr. Colp called him in and said, "Dreiling, you can join me in my office and make a lot of money, or go into the lab and do research on biliary and pancreatic physiology. You'll get only $600 a year. Take your choice." Dr. Dreiling made his choice, and several books and 260 papers later, praised the foresight of the man who, though a brilliant clinical surgeon, understood the inadequacy of the scalpel in solving complex physiologic problems (20).

Dreiling added the secretin test "to the diagnostic armamentarium of the Hospital" after a preliminary series of 93 controls and 52 patients with disease, using different sources (Astra, Wyeth) of secretin (21). Dreiling and Hollander then expanded the control series to 172 and used proper statistical analysis to provide a normal range for 80 min volume, maximum bicarbonate concentration and amylase concentration, and calculated that data scatter (represented by coefficient of variation) would be minimized by expressing outputs on a per kilogram basis and using Lagerlof's 80 min collection rather than shortening it to 40 min (22).

In his third study, in which duodenal aspirate was also analyzed for icteric index, Dreiling (by now a George Blumenthal Jr. Fellow) found that of 98 patients with complaints after cholecystectomy, only two had abnormal pancreatic secretion (one with carcinoma and one with chronic pancreatitis). Responses in four other patients with a biliary pigment were suggestive of surgically remediable organic common duct obstruction (23). A series of papers reported studies on patients with obstructive jaundice, pancreatic insufficiency and cholecysto-enteric anastomosis (24), tumors in and about the pancreas, diabetes mellitus (25), and pancreatitis and various gastrointestinal diseases (26). The normal ranges for pancreatic secretion after Lilly secretin (> 2.0 mL/kg, HCO_3^- > 90 mEq/L, amylase > 6 U/kg) were established in 123 controls (27) and, unlike gastric secretion, were little affected by sex or age (28).

When potent injectable pancreozymin became commercially available (Boots, Vitrum) this enzyme-stimulating hormone was injected before the secretin (29). "Sporadic attempts at cytologic examination of duodenal aspirates had been made in this laboratory since 1948, when the first case of cancer of the pancreas had been diagnosed by demonstrating cancer cells on the duodenal smear, but a systematic investigation was not possible until the cooperation of a trained cytologist (H.E.N.) was available at the hospital" (30). Provocative blood tests (the serum amylase response to morphine, secretin, methacholine and bethanechol singly and in combination) were of no value in the diagnosis of pancreatic disorders (31).

Dreiling's classification of pancreatic deficiency states remained little altered for over 30 years:

- *Total insufficiency* (low volume, bicarbonate, enzyme) indicated extreme destruction, as in end-stage pancreatitis or advanced pancreatic cancer;

- *Qualitative insufficiency* (low bicarbonate concentration with normal flow) indicated chronic pancreatitis;

- *Quantitative insufficiency* (low flow with normal bicarbonate and enzyme concentrations) indicated ductal obstruction, as in pancreatic cancer;

- *Isolated enzyme deficiency* (with normal flow and bicarbonate) was seen in nutritional pancreatic fibrosis, sprue and inflammatory bowel disease;

- *Hypersecretion* indicated hypertrophy and hyperplasia of the hepatic and ductal systems, as in cirrhosis and hemochromatosis (29, 32–34).

As for the pancreozymin-secretin test (32): "The combined test was discontinued after 1000 tests because of the additional expense, more frequent reaction, the equivalence of information, and the lack of availability of CCK-PZ for clinical use in the USA."

The international reputation of The Mount Sinai Hospital for pancreatic research was recognized when the 1970 World Congress of Gastroenterology selected Dreiling to give one of the Quadrennial Reviews, initiated at this Copenhagen meeting, on "The early diagnosis of pancreatic cancer" (35). The data on 401 patients with pancreatic cancer showed 95% accuracy for carcinoma of the head of the pancreas, but decreasing accuracy for the body (83%) and the tail (81%). Cytologic accuracy was 82%, 89% and 75% for these parts of the pancreas. "Further refinements in exocrine secretory techniques, such as newer stimulants, altered protocols, and augmented secretory capacity, may complicate the testing but are not likely to provide much more significant data. Let me conclude with the prediction that accuracy and early diagnosis are most likely to result from advances in pancreatic scanning. . . ." (35), a prediction fully justified by our current ultrasound, CT, MRI, angiography and serologic tests.

Pancreatic Physiology

Although pancreatic secretion became a routinely available diagnostic test at Mount Sinai, research in gastrointestinal physiology assumed greater importance, especially after the return of Dr. Henry Janowitz in 1948 after World War II. Neither vagotomy (36), histamine, histalog (37) nor glucagon (38) had any direct effect on pancreatic secretory flow, bicarbonate concentration or enzyme output. However, the carbonic anhydrase inhibitor acetazolamide (Diamox) given intravenously to dogs led to 95% inhibition of secretin-stimulated duodenal juice volume and 60% inhibition of bicarbonate secretion (39); there were similar marked inhibitions of duodenal juice volume (40), and hepatic bile output (41) in man. Dreiling and Janowitz's studies of the secretion of electrolytes (42, 43) in the above studies and in those where various anticholinergic piperidyl drugs inhibited fluid but not bicarbonate concentration (44), led them to the following conclusions at the 1962 Ciba Symposium (45): (1) specialized cells of the pancreas secrete HCO_3^- by an active transport mechanism whose nature is unknown at present; (2) the HCO_3^- of pancreatic juice is derived in part from metabolic CO_2 and in part from the HCO_3^- of the blood; (3) carbonic anhydrase activity is required for high rates of secretion; (4) the carbonic anhydrase functions in part to maintain a critical intracellular pH-CO_2 range; and (5) probably as the HCO_3^- solution moves down the collecting system it undergoes an exchange with Cl^- of the interstitial fluid or blood (the existing concentrations favoring this).

Pancreatic Secretion in Animals

It was impossible to study pure pancreatic duct juice uncontaminated by biliary and intestinal secretions in human subjects until the introduction of endoscopic retrograde cholangio-pancreatography (ERCP); thus, the human studies described above were of duodenal aspirate. Dogs can be equipped with a chronic duodenostomy cannula through which the papilla of the pancreatic duct can be cannulated under direct vision with a bent glass capillary tube. This Thomas and Crider technique (46) was used for many years at Mount Sinai and was described in detail by Hollander's group (46).

While enzyme secretion of the pancreas had long been known to be stimulated by the vagus nerves, the bicarbonate and water outputs were usually attributed to stimulation by secretin, so that increases in both volume and bicarbonate secretion of secretin- or histamine-stimulated pancreatic juice after supradiaphragmatic vagotomy suggested that the vagi do contain inhibitory fibers (47).

When I came to work with Dreiling and Janowitz in 1961, I suggested that the commercial availability of the more purified Jorpes-Mutt preparation of secretin from Vitrum provided an opportunity to attempt to evoke a maximum (alkaline) bicarbonate output of the dog pancreas analogous to the maximal acid response of the stomach (I had been researching this in England, by measuring peak acid output [48, 49] using Kay's novel augmented histamine test [50]). With Claude Perrier of Geneva we did achieve maximum bicarbonate output with either single intravenous injections or continuous intravenous infusions of secretin, and we were able to produce inhibition by supramaximal doses (51).

We showed that the dog pancreas could secrete about one-third as much alkali as the stomach could secrete acid (52). There was, however, no significant correlation between maximum bicarbonate output and maximum acid output (52). Nevertheless, there was a highly significant correlation between maximum bicarbonate output and weight of pancreas (52), a finding studied by Jack Hansky and Oswaldo Tiscornia (53), who concluded that the female dog pancreas could secrete 0.08 mEq bicarbonate/g, a figure identical to that found in normal female human subjects. Hansky and Tiscornia also achieved maximum amylase output with either single intravenous injections or continuous intravenous infusions of pancreozymin (Cecekin, Vitrum) (54). Moreover, a combination in a single injection of a maximal pancreozymin dose with a maximal secretin dose evoked the maximal amylase, fluid and bicarbonate secretory capacity of the pancreas (54).

The Augmented Secretin(-Pancreozymin) Test

There was no general agreement on whether the diagnostic discrimination between normal subjects and patients with chronic pancreatitis would be better with a submaximal or a maximal dose of secretin. Agren and Lagerlöf (55) injected 3 cat units kg: "We have chosen this as our standard dose since there are reasons to believe that in pathological conditions . . . a subnormal function will be easier detected after submaximal stimulation." With the demonstration of a maximum bicarbonate output of the dog pancreas, it was suggested that "the measurement of maximum secretory capacity in man may allow more quantitative assessment of secretory impairment" (51).

There have been many human studies of this augmented secretin test with the proprietary Boots preparation, the Vitrum preparation or pure G.I.H. (GastroIntestinal Hormone, Karolinska Institute) secretin given as a single injection or as a continuous intravenous infusion. Dreiling's group compared the standard with the augmented secretin test in 366 patients (56). In 130 without pancreatic disease, the mean (SD) volume response doubled from 3.2 (0.6) to 6.3 (0.9) mL/kg, with the lower limit of normal (LLN) also doubling from 2.0 to 4.5 mL/kg. The maximum bicarbonate concentration increased only slightly, from 110 (10) to 117 (12) mEq/L and its LLN from 90 to 93 mEq/L, and output from 21.6 (4.7) to 40.7 (9.1) mEq/80 min and LLN from 12.2 to 22.5. The amylase secretion increased markedly from 21.4 (7.4) to 36.7 (14.2) U/kg and its LLN from 6.6 to 8.3 U/kg. However, in patients with pancreatic insufficiency, volume flow and bicarbonate secretion did not increase to the same degree as in normal subjects, and in patients with pancreatic cancer there were no significant increases in flow or bicarbonate with the augmented dose of secretin. Thus, the augmented secretion test both corroborated and enhanced the diagnostic discrimination of the standard test.

Some studies suggested that an augmented secretin test of maximal or near maximal bicarbonate output did improve diagnostic discrimination (57, 58). In one small series, we found that peak bicarbonate output in response to either a submaximal or near-maximal dose of secretin provided absolute discrimination between 10 male control subjects and five men with chronic pancreatitis (59). In Norway, full dose-response studies in healthy volunteers and in patients with chronic pancreatitis showed that diagnostic discrimination was better with a G.I.H. dose of 0.7 clinical units/kg/hr than at lower or higher doses (60).

Interpretation of Secretin Tests

A low volume even with normal concentrations suggests a carcinoma. Low concentrations even with a normal volume indicate chronic pancreatitis. The combination of a low volume and low concentrations of bicarbonate and enzymes expresses severe exocrine insufficiency. Hypersecretion may occur in some phases of pancreatitis, hemochromatosis and cirrhosis. Diagnostic discrimination may be improved by considering volume and bicarbonate concentration together, or by calculating bicarbonate output. Wormsley has emphasized that the bicarbonate concentration should always be assessed in conjunction with the secretory rate (57). A high bicarbonate concentration denotes a normal bicarbonate secretory capacity. I found that with high rates of secretion in response to large doses of secretin, the bicarbonate concentration may decrease as the volume increases (61), so that a low bicarbonate concentration does not denote a low secretory capacity unless the volume is also low. Wormsley has also re-emphasized that a low bicarbonate output may represent a small response from a normal gland with a high threshold or low sensitivity to hormonal stimuli; only if a repeat test with a near-maximal stimulus results in a low output can the pancreas be definitely classed as abnormal.

Let Dreiling have the last word (56): "In clinical practice a standard secretion test is sufficient when normal results are obtained. If a low or borderline volume or maximum bicarbonate response is encountered, the standard test should be followed by an augmented test with the expectation that any questionable abnormality in secretion will not only be confirmed, but enhanced."

Gastric Acid and Pancreatic Alkali

It has long been appreciated that the pH in the human postbulbar duodenum normally remains neutral in spite of being exposed to several liters per day of gastric juice of pH about 1. But the relative neutralizing powers of food and antral, duodenal, jejunal, biliary and pancreatic secretions were uncertain. Once measurements of maximal secretory capacity of both the stomach (50) and the pancreas (51) become available, the hypotheses that pancreatic secretion might be correlated with, and/or neutralize gastric secretion could be tested. In the two Mount Sinai studies, maximum bicarbonate output of the dog in response to secretin alone ranged from 2.4 to 4.6 (mean 3.3) mEq/15 min (51) and to secretin and pancreozymin from 2.6 to 4.3 (mean 3.2) mEq/15 min (54). Thus, bicarbonate outputs expressed as a proportion of maximum acid output in the same dogs ranged from 19–45% (mean 30%) (52), a proportion similar to the one-third found in dogs by Preshaw and Grossman (62). Although Perrier and I (51) found no significant correlation between maximum bicarbonate and acid outputs in the dog, on my return to London I was able, with Gutierrez, to find a correlation in humans. Bicarbonate secretory capacity in patients with duodenal ulcers was normal and comparable to gastric acid secretory capacity (63). We found that the basal bicarbonate output of the duodenal aspirate in patients with duodenal ulcers was only half that of control subjects, and suggested this might lead to decreased neutralization of gastric acid in the duodenum.

Hypersecretory States

Certain patient groups showed marked hypersecretion of volume and bicarbonate output (64). In patients with Zollinger-Ellison syndrome these are doubled, presumably due to the high acid load entering the duodenum (and thus increased release of secretin), together with the pancreas-stimulating effect of the ectopic gastrin. In hemochromatosis, these outputs may be triple normal, suggesting either increased sensitivity of the ductular parenchyma to secretion or increased ductular cell mass. However, in patients with cirrhosis, part of the hypersecretion must come from increased output of bicarbonate in bile from the hepatic ductular system.

Pancreatitis

At the end of the 19th century, Manges reported a woman of 21 with an acute abdomen, found at laparotomy by Dr. Gerster to have acute pancreatitis with fat necrosis. She was only the fourth patient in the literature "in which recovery has followed operative interference in acute pancreatic disease" (65). Half a century later, Dreiling and Janowitz extended their physiological measurements of pancreatic exocrine secretion in man and dog toward the study of the etiology and pathogenesis of pancreatic inflammation. Much of this work was summarized in the 1962 Ciba symposium (45) and their 1964 monograph (66).

These studies were occasionally clinical. Thus, from 1945 to 1959, 417 patients were admitted to Mount Sinai with pancreatic cancer as well as 100 with chronic pancreatitis (51 with biliary disease and 33 with alcohol excess), of whom 24 had calcinosis: six of these 24, and none of the 76 without calcinosis, had pancreatic cancer (67). In the dog, calcium was secreted not with the secretin-stimulated electrolyte component, but with the pancreozymin-stimulated enzyme fraction (68). The chronic effects of alcohol on the pancreas had been extensively studied elsewhere, but acute intravenous infusions of alcohol in dogs, in doses giving comparable blood levels (25 – 29 mg/100 mL) to those in human drinkers, produced prompt and marked inhibition of flow rate and bicarbonate concentration. This was thought to be due to an effect on the electrolyte transport systems (69). Patients with chronic pancreatitis with typical low post-secretion volume and bicarbonate concentration showed differences by etiology: those with biliary tract disease had higher volume and bicarbonate concentrations than those with alcoholic pancreatitis (64). Most interesting were alcoholics with no symptoms or signs of either hepatic or pancreatic diseases; they showed high volume with lower bicarbonate concentration, that is, pancreatic hypersecretion (64). This pancreatic hypersecretion also had been found in patients with cirrhosis and hemochromatosis (see above). It was suggested that this hypersecretion might represent an "initial reaction of the pancreas to injury, normally ductular reduplication and hypertrophy. As the inflammation and fibrosis continues, the increased flows return towards normal . . . accompanied by a marked fall in bicarbonate concentration. The final stage of low flow, low bicarbonate, and low enzyme secretion, corresponds . . . to the more advanced . . . fibrosis, atrophy and calcification" (64). Of 17 alcoholic patients who underwent secretin tests annually for 10 years, in 11 patients who continued to drink, the observed early increased flow rate returned to normal in 2 – 3 years and then, together with the bicarbonate concentration, continued to decrease. In the six patients who stopped drinking, these measurements increased (64, 70), suggesting pancreatic ductular cell regeneration after injury.

This problem of pancreatic regeneration was pursued in the dog, in which (as in man) obstruction of the pancreatic duct leads to atrophic degeneration. Immediate microsurgical reanastomosis of a cut pancreatic duct prevented these changes. If ductal reconstruction was satisfactorily performed, then exocrine secretion, histology and pancreatography recovered within 13 to 44 days after the duct was cut (71, 72). This exocrine functional recovery after ductal decompression, alloxan (73), and ethionine (74), led Dreiling and his colleagues to give an affirmative answer to their rhetorical question (75), "Does the pancreatic gland regenerate?"

Further dog studies tested the Janowitz and Dreiling preference for the exchange rather than the admixture model of the ionic composition of pancreatic juice (45). For the sum of Cl^- and HCO_3^- to be constant, yet Cl^- to vary inversely with HCO_3^- then the isotonic primary HCO_3^- secretion must be altered by either an exchange of luminal HCO_3^- for interstitial Cl^- in the ductular system, or an admixture with a low HCO_3^- concentration interstitial fluid. Both stop-flow (76) and duct perfusion (77) studies showed both loss of HCO_3^- and increases in Cl^- consistent with the exchange hypothesis.

Various metabolic and endocrine effects on exocrine pancreatic secretions were studied in animals and man at The Mount Sinai Hospital (78). A ten-year follow-up of a patient with type V hyperlipoproteinemia observed both recurrent attacks of abdominal pain and progressive impairment of pancreatic juice volume, bicarbonate concentration and enzyme output (79). Hypophysectomy in the dog depressed maximally stimulated pancreatic function, and this suppression could be partly reversed by administration of ACTH or corticosteroids (80), just as the decreased exocrine maximal outputs after bilateral total adrenalectomy were partly corrected by intravenous aldosterone (81).

Although the Mount Sinai researchers focused on the volume flow and bicarbonate concentration and output, amylase was also studied, as were other enzymes such as desoxyribonuclease I (82). Amylase in serum was confirmed as electrophoretically heterogeneous, with a probable hepatic component not reduced by pancreatectomy (83); moreover, the elevated amylase in acute pancreatitis could be partly due to reduction of a normally present amylase inhibitor (82). False positive diagnoses of acute pancreatitis due to macroamylasemia could be avoided by also measuring urine amylase and creatinine routinely and calculating the amylase-creatinine clearance ratio (84).

The phenomenon of hyperlipemia in acute pancreatitis, whether in patients or experimental animals, was studied by Jacques Kessler (85), who demonstrated lipoprotein lipase (LPL) activity in canine pancreas and in pancreatic juice and the juice LPL stimulated by secretin and pancreozymin administration. However, LPL activity increased with progressive dilution of the juice, suggesting the presence of an inhibitor and raising the possibility that pancreatic necrosis either releases an inhibitor which interferes with the normal clearing mechanism of plasma triglycerides or releases a source of LPL.

Comment

In the early years of this century and again from the mid-1940s to the 1970s, Mount Sinai gastroenterologists had a major interest in the pancreatic physiology and pathophysiology of acute relapsing and chronic pancreatitis and carcinoma. However, in recent years, pancreatic research elsewhere has moved to imaging and tumor markers with improvement in early diagnosis even if these did not lead to great changes in medical or surgical treatment.

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16

The History of Liver Disease at The Mount Sinai Hospital

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Abstract

Diseases of the liver and biliary tract interested the physicians of The Mount Sinai Hospital from the time the hospital started until the present. Indeed, the institution has become a well-recognized center for the study of the liver and its diseases. During the first 75 years of the hospital, there were many admissions for hepatobiliary diseases, resulting in many case reports. The evolution of the hospital into a teaching hospital brought with it a more systematic method of studying diseases, not only in Pathology under Paul Klemperer, but in Clinical Chemistry and Microbiology as well. Liver biopsy was also attempted. With the arrival of Hans Popper in 1957, the emphasis shifted to coordinated studies of both normal and abnormal liver structure and function in diseases. Soon, Liver Diseases (Hepatology) was split from Gastroenterology, with Fenton Schaffner as the first chief. Over the next 30 years, more than 1000 papers, chapters and books were published. The main areas of research were fibrosis, cholestasis (especially morphology and bile salt metabolism), toxic liver injury, metabolic transformations and carcinogenesis. Primary biliary cirrhosis and viral hepatitis were and continue to be special interests. Fellows from all over the world were trained and many moved on to leadership positions. Although he was active in the development of the liver transplant program, Popper did not live to see its start. A new generation of hepatologists maintains the interest and position of The Mount Sinai Hospital in this important field of medicine. **Key Words:** Liver disease, history, The Mount Sinai Hospital.

LIVER DISEASE had been an uncommon reason for admission to The Mount Sinai Hospital in the first one hundred years of its existence, but this has changed in the last fifty years. The Mount Sinai 100th anniversary issue of the *American Journal of Medicine*, published in November 1952 with George Baehr as guest editor, contained reprints of what were considered the most significant contributions to medicine from the hospital. None was related to the liver. Included in this issue of the *American Journal of Medicine* were an informative forward by Baehr and an article on the founding and the early days of Mount Sinai, written by Eli Moschcowitz.

The first recorded death from liver disease at Mount Sinai was in 1861 from primary hepatocellular carcinoma. The decade 1897 – 1907 saw a total of 67 patients with such tumors admitted to the hospital, while in 1986 – 1995, 183 were admitted. However, 890 patients with hepatobiliary diseases were hospitalized from 1897 – 1907, while in the recent last decade, 4347 were admitted. During the 19th century, contributions from Mount Sinai to the medical literature concerning liver diseases consisted of case reports of unusual conditions or unusual presentation of common diseases, mainly cysts and abscesses. Two were in the newly established *Mount Sinai Hospital Reports*, which first appeared in 1899 (1, 2). This became the *Journal of the Mount Sinai Hospital* in 1933. Between 1900 and 1904, four cases of rapidly fatal liver disease, termed acute yellow atrophy, were seen in young women (3, 4). Despite careful study and autopsy examination, no cause was found, although pregnancy may have been a factor in two. Such individual case reports of unusual cases of liver diseases have continued to appear, albeit less frequently. Series of cases were reported soon after the turn of the century (5, 6). Now very large series, natural history studies, controlled trials and experimental

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data related to the liver make up the bulk of publications, in addition to books, book chapters and periodicals.

Many factors contributed to the shift in direction of the role of Mount Sinai in hepatology. The first was that the institution became a teaching hospital at the turn of the 20th century, with the start of an intern training program. Medicine, surgery and pediatrics were established as separate disciplines, with the development of the "giants" of the hospital's history, including Albert Berg in Surgery, Emanuel Libman in Medicine and Abraham Jacobi in Pediatrics, to name just a few. Chronic jaundice in those days was considered to be obstructive in nature and mainly a surgical condition (7).

Shortly after Word War I, Paul Klemperer was appointed as the first full-time chairman of the Department of Pathology. This was a second factor in the development of interest in liver diseases at Mount Sinai. Klemperer and his coworker, Sadao Otani, began to describe hitherto unrecognized conditions, first in the innovative clinical pathological conferences published in the *Journal of the Mount Sinai Hospital* or its predecessor. Collections of some of these unusual cases led to the establishment of lupus erythematosus, thrombotic thrombocytopenia, giant follicular lymphoma and regional enteritis as disease entities. Klemperer described chronic intrahepatic obliterating cholangitis but did not connect this condition with inflammatory bowel disease (8). Rare tumors of the liver like primary sarcoma were reported (9) and primary hepatocellular carcinomas were the subject of clinical pathological conferences (CPCs) reported in the *Journal of the Mount Sinai Hospital* (10). Numerous cases of parasitic diseases of the liver and abscesses also were published in *The Journal* in the form of case reports or CPCs. Jaundice in heart failure was ascribed largely to hepatic anoxia (11), but three years earlier pulmonary infarction with excess bilirubin production was blamed (12). Arthur Sohval wrote an extensive review of hepatic complications of polycythemia vera, including descriptions of hepatic and portal vein thromboses, and the appearance of cirrhosis in some cases (13). Adverse hepatic drug reactions were beginning to be recognized, especially with cinchophen (14) and arsenicals (15) and experimental production of these in laboratory animals was attempted (15, 16). Reuben Ottenberg and Rose Spiegel compiled a detailed description of jaundice due to various chemicals, which served as the standard reference on the subject for many years (17).

A third factor contributing to the establishment of hepatology at Mount Sinai was the utilization of the clinical chemistry and later, the microbiology laboratories, in a systematic fashion. This was part of the global trend of moving away from empiricism to scientific medicine. Nitrogen metabolism was studied at various stages of medical and surgical hepatobiliary diseases (18) and in the hepatorenal syndrome (19, 20). Early attempts were made to investigate bilirubin and bile salt metabolism (21). New laboratory tests for assessing liver function were evaluated (22). One interesting test detected benzoyl glucuronide after administration of hippuric acid (23). This was devised by Isidore Snapper, who arrived from China in the early years of World War II. He had previously described the test for and significance of direct and indirect bilirubin with van den Bergh in Amsterdam just before the First World War. Snapper never associated glucuronide formation with bilirubin metabolism, although he lived to see direct bilirubin discovered to be bilirubin glucuronide. Mount Sinai joined the debate about whether catarrhal jaundice was the result of inflammation of bile ducts or necrosis of liver cells (24). The role of medications such as arsphenamine (25) and cinchophen (26) in causing jaundice that resembled hepatitis was explored. Just prior to World War II, attempts were made to biopsy the liver percutaneously by Edgar Baron (27) and just after the war by punch at surgery by Edward Jemerin (28). Percutaneous needle biopsy at this time did not succeed because bleeding could not be adequately predicted or controlled. The war itself offered the opportunity for the many Mount Sinai physicians in military service to see numerous cases of hepatitis, no longer called catarrhal jaundice and recognized to be either infectious or transmitted via serum. The heightened interest in liver disease resulted in the publication of the first large American textbook on diseases of the liver by Solomon Lichtman, which appeared shortly after the war. It went through three editions and was the standard mid-century text on the subject (29). A liver clinic was started as an adjunct to the GI clinic, with Alexander Richman as chief and Albert Parets as his associate.

The Popper Era

The next important factor in the growth of interest in liver disease at Mount Sinai was the appointment in 1957 of Hans Popper as chairman of the Department of Pathology after Klemperer's retirement. A few months later, Popper brought

Fenton Schaffner to New York to provide the clinical arm for a growing liver team forming in Pathology. The aim of the group was to correlate structure and function in the various liver diseases. Popper had been investigating many clinical and pathologic aspects of liver diseases for more than 20 years, first in Europe under Hans Eppinger in Vienna and then in Chicago where he was the pathologist for the Cook County Hospital. Schaffner was first a Fellow in Pathology at Cook County under Popper and then a part-time colleague while in full-time internal medical practice. Together they had just published a new type of text on liver, *Liver: Structure and Function* (McGraw-Hill, 1957), which emphasized structure as a guide to function.

The liver team was assembled and functioning, and research grants began to be received. Areas developed included histochemistry with recruitment of Tibor Barka (who became the first editor of the *Journal of Histochemistry*), biochemistry with Edward Singer and Ferenc Hutterer, immunocytochemistry with Fiorenzo Paronetto, and electron microscopy with Schaffner, under the tutelage of the Cell Research Laboratory headed by Leonard Ornstein. The number of liver biopsies performed in the hospital increased dramatically to about 600 a year with the introduction of the Terry Needle, brought from Chicago. The biopsy specimens were processed with great care by Hendrika van der Noen, who also trained many technicians in preparing truly beautiful histologic slides that remain the mainstay of teaching and research as well as diagnosis.

The Popper years saw an explosion in description and discovery, and in the number of papers published, which amounted to more than 1000 in a period of 30 years. The main topics were hepatic fibrosis, cholestasis with special emphasis on morphology and bile salt metabolism, toxic liver injury, metabolic transformations, and carcinogenesis. The early work of the team was described in annual progress reports from 1960–1963, which appeared in volumes 27–30 of the *Journal of the Mount Sinai Hospital*. These reviews dealt mainly with our work in hepatic fibrosis and the development of chronicity of liver disease. Later reviews were published in each volume of *Progress in Liver Diseases*.

The studies of fibrosis revealed that as collagen increased, it was distributed around portal tracts, proliferating ductules, and sinusoids in the spaces of Disse (30). The perisinusoidal fibrosis was associated with the formation of a basement membrane, resulting in capillarization of the sinusoids (31). The fibrosis of schistosomiasis was found to be periductal (32) and resulted in presinusoidal portal hypertension (33). Detail of the structure of the ductule was described, including how it acted as a trellis for the deposition of collagen (34, 35). Various aspects of alcoholic (36, 37), autoimmune (38, 39), and later, viral chronic liver disease (40, 41), were explored, including clinical and chemical correlations. Drug-induced liver disease was classified as hepatic or cholestatic (42), and many publications followed, ranging from case reports to large series and reviews. Ultrastructural and histochemical aspects of Wilson's disease were detailed (43) and experimental copper intoxication was studied (44). Involvement of the liver in AIDS was investigated as the epidemic progressed (45, 46). Much attention was devoted to cholestasis (47). The morphology of the condition was examined in patients in whom a bile duct had been ligated (48, 49) and in animals to which lithocholate was administered (50), as well as in those given cholestatic drugs (51) and alpha naphthylisothiocyanate (52). The site of the initial injury in primary biliary cirrhosis (53) and the stages of the disease (54) were described. Immunologic markers of the disease were studied (55). A large series of patients with primary biliary cirrhosis was accumulated, enabling description of the natural history (56), serum bilirubin as a prognostic indicator (57), and the effects of treatment in trials including penicillamine (58), colchicine (59) and later ursodiol and methotrexate. The serum bilirubin level also proved to be a prognostic marker for sclerosing cholangitis (60). The role of the bile acids in causing cholestasis and in producing hepatocellular injury (61) was examined. The state of the art facilities assembled also permitted a search for a no-effect level of toxic substances (62) and the earliest indications of hepatic injury and malignant transformation (63). The substances examined had either military (intravenous fat emulsions [64] and space cabin atmospheres [65]) or environmental importance (pesticides [66], vinyl chloride [67]).

A steady stream of foreign fellows and visitors began arriving, beginning with Perez from Argentina, Pang from Indonesia, Scheuer from England, and many more. Giorgio Menghini visited Mount Sinai in 1958 at the time the first meeting of the International Association for the Study of the Liver was held in Washington. Popper was a founding father of this society, which was modeled after the American Association for the Study of Liver Diseases (AASLD), which Popper founded a decade earlier in Chicago. Menghini brought his newly-invented aspiration liver biopsy needle and performed the first such biopsy at Mount Sinai. He left one of his needles and Schaffner performed the second such one-second biopsy on a young diabetic girl in ketoacidosis who suddenly developed massive hepatomegaly and ascites. This was reported as a case of excessive glycogen deposition in the liver, visualized by electron microscopy (68). Albert Parets reviewed our early experience with the needle (69), which we continue to use to this day. The team and the visitors began producing a torrent of more than 500 papers, as well as frequent presentations at national and international meeting which continued for more than 30 years. The work continued even while Popper was Dean and President of our new medical school; he was the main driving force in its foundation.

Popper and Schaffner edited a special issue of *Gastroenterology* devoted to liver diseases in November 1959. As a result of this special issue, the series, "Progress in Liver Diseases," was begun in 1961, published by Grune and Stratton. It went through nine volumes, the last published by Saunders. One volume appeared every three years, until after Popper died in 1988. Other books appearing were *Clinico-Pathological Conferences of The Mount Sinai Hospital* by Schaffner and Popper, published by Grune and Stratton in 1963; *Cirrosis Hepática* by Anibal Latuff (from Venezuela) and Schaffner, published by Editorial Científico Médico, Barcelona in 1966; and *The Liver and Its Diseases*, put together as a festschrift for Popper's 70th birthday by Schaffner, Sheila Sherlock (of London) and Carroll Leevy of (New Jersey), published by Intercontinental Medical Books in 1983. Popper and Schaffner contributed chapters to the third and fourth editions of Bockus' *Gastroenterology*, Schaffner being an associate editor in the fourth edition and a senior co-editor in the fifth. Popper was an associate editor for the first two editions of *The Liver: Biology and Pathobiology*, published by Raven Press, with Irwin Arias as senior editor. Popper also served as an associate editor for *Gastroenterology* and for *Hepatology*.

During the Popper era, a program project grant was awarded by the National Institutes of Health (NIH) to Pathology to cover much of the research activity. A training grant for liver fellows was also awarded and Alexander Gutman, the chairman of the Department of Medicine, split Liver Diseases from Gastroenterology in 1965 and created a separate division with Schaffner as the first chief. One or two Liver fellows were trained each year and when the grant ended, the hospital funded the fellowship and continues to do so. Several fellows elected to stay at Mount Sinai for varying periods of time. Franklin Klion remained as a full-time clinician for several years and then went into private practice. He continues to maintain close ties to the Division of Liver Diseases and when Richman retired as chief of the Liver Clinic, Klion was his successor. He also takes a very active role in the transplant program, and wrote a book, *Guide to Liver Transplantation*, with Thomas Fabry, published by Igaku-Shoin in 1992. Popper trained many pathologists from all over the world and several have become chairmen of their own departments, including Stephen Geller, Michael Gerber and Emanuel Rubin in the United States, Peter Scheuer and Helmut Denk in Europe, Zilton Andrade in Brazil and Goruku Ohta in Japan. They have all achieved international reputations and retain an active interest in the liver. Swan Thung was also a Popper student and she inherited the job of being responsible for all the liver biopsies as well as immunologic studies involving the liver, which she is still doing. Several internists from abroad also spent time learning about liver disease in the Department of Pathology and then returned home to become chiefs of their medical departments. These included Massimo Colombo in Italy, Whan Kook Chung and, later, Boo Sung Kim from Korea, and Hiroshi Sasaki from Japan. Many specimens of liver tissue were sent to Mount Sinai for second opinions and a very large collection of slides with accompanying histories was accumulated. After Popper died, these were donated to the Armed Forces Institute of Pathology in Washington.

Popper received many honors, including several honorary doctoral degrees. One was from the University of Vienna, his alma mater, on the 600th anniversary of the founding of the institution. The school also renamed the pathology department the Hans Popper Institute of Pathology. The Hans Popper Primate Center in Orth, a suburb of Vienna, was dedicated in 1992 for the study of viral diseases, including hepatitis. He received numerous honors in the United States. The Friedenwald Medal was bestowed on him in 1971 by the American Gastroenterological Association (70). Popper was elected to the Academy of Arts and Sciences. He spent the year 1974 as a Fogarty Scholar in residence at the NIH in Bethesda after he stepped down as dean and president. During his year away, he was able to organize a meeting on nomenclature chaired by Carroll Leevy of New Jersey. The meeting resulted in a book on standardization of nomenclature, diagnostic criteria and diagnostic methodology (71).

Mount Sinai named the department of pathology the Popper and Stratton Department of Pathology, Lillian and Henry Stratton being major benefactors and close friends. Dr. Popper was awarded the Jacobi Medallion in 1973. Thomas Chalmers, Popper's successor as dean and president of the Medical Center, received the medallion in 1981, while Schaffner received it in 1992 (Fig. 1). Popper was very active in the national and international liver associations, having served as president of both the American and international societies. Chalmers (before he came to Mount Sinai), Schaffner and Paul Berk also were AASLD presidents. Berk, Schaffner and Rudi Schmid of California produced a book honoring Popper entitled *Hans Popper, a Tribute*, published by Raven Press in 1992. This was also translated into German as *Hans Popper, Freunde Erinnern Sich*, published by Schattauer. Herbert Falk, who founded the pharmaceutical firm devoted mainly to hepatological and gastrointestinal medications, paid for and distributed the book. Falk and Popper were close friends, and Popper served as an important advisor to Falk. For forty years, Falk sponsored many of Popper's symposia and other teaching activities that promoted interest in liver diseases. Falk has honored this relationship by creating the Hans Popper Prize for outstanding work in the field; it is awarded during the triennial Basal Liver Week.

Chalmers, who succeeded Popper as dean and president in 1974, was responsible for introducing the liver team to randomized, double-blind, controlled trials of therapy for liver diseases. Berk came to Mount Sinai as chief of Hematology, from NIH, where he was Chalmer's successor as chief of the liver program. He put together a team and laboratories dedicated mainly to bilirubin and membrane transport in the liver. During the Popper era, in 1980, two journals devoted to the liver were founded in the United States. AASLD gave birth to *Hepatology*, with a big push by Popper. Many of the Mount Sinai team served on the editorial board. The second journal, *Seminars in Liver Diseases*, began and still is at Mount Sinai, with Berk as editor and Chalmers, Charles Lieber, Popper and Schaffner constituting the original editorial board. Both journals continue to flourish and Berk has just completed a six-year term as editor of *Hepatology*. Lieber, who works at the Bronx Veterans Administration Hospital, has been editor of *Alcoholism*. When Schaffner became emeritus in 1991, Berk became the second chief of the division and the laboratories he established in the Division of Hematology came with him to Hepatology.

Fig. 1. Hans Popper, Thomas Chalmers, and Fenton Schaffner (l to r), together at a Mount Sinai School of Medicine conference in 1973.

The Transplantation Era

The year 1988 marked the end of the Popper era with his death at the age of 83 from pancreatic cancer. It also marked the introduction of liver transplantation at Mount Sinai. Within a few years, under Charles Miller, the institution became the third largest transplant center in the country. Both Popper and Chalmers pushed hard to have a transplant program at Mount Sinai. They did this, with the help and blessing of Arthur Aufses, Jr., the chairman of the Department of Surgery (Fig. 2). The trustees and the administration of the medical center gave their enthusiastic support for the program.

The first liver transplantation at Mount Sinai occurred on September 3, 1988, involving a patient with sclerosing cholangitis. The 1000th transplantation was done on October 9, 1995 and the 1000th patient was transplanted on September 18, 1996. As of September 1996, 2868 patients had been evaluated for transplantation and 254 were on the waiting list. The youngest surviving patient at transplant was not quite six months old and the oldest was 75 years. Several living-related and split-liver transplants have been performed. These data were obtained from the Fall 1996 issue of *Transplantation Update*, a publication of the Division of Liver Transplantation of the Department of Surgery.

After transplantation was begun, the need for more help from the Division of Liver Diseases

Fig. 2. The original Mount Sinai Liver Transplant team. First row (l to r): Fenton Schaffner, Arthur Aufses, Charles Miller, Paul Berk; Second row (l to r); Nancy Bach (medical Liver Fellow), Elizabeth Harrington, Myron Schwartz, Margaret Kadian (first coordinator), Martin Harrington (transplant Surgical Fellow) and Angelina Korsun (first administrator).

became obvious. Nancy Bach, then the liver fellow when transplantation began, was the one who set the tone for the cooperation of the division with the transplant team. Bach remains a full-time clinician with the division. Not only were more fellows needed, but more supervision and training had to be provided. To supervise the training as well as the clinical activity of the division, Henry Bodenheimer was invited to return to Mount Sinai. He had been an intern, medical resident and liver fellow at the hospital from 1975 to 1979, after which he went to Providence to finish his training in gastroenterology and then join the Brown Medical School faculty. More fellows and several full-time faculty members were recruited. During his fellowship and while he was in Rhode Island, Bodenheimer participated with Schaffner in clinical trials of therapy for primary biliary cirrhosis and conducted multi-center investigations including Mount Sinai. He participated in national trials of interferon treatment of chronic viral hepatitis, work he continues to this day.

Increasing clinical responsibilities, mainly related to the active transplant program, and a decrease in funding from government and other sources have curtailed some of the research activity. Nevertheless, studies of primary biliary cirrhosis (72, 73), chronic viral hepatitis (74, 75), nonalcoholic fatty liver (76), and acquired immunodeficiency syndrome (77) continue, as do investigation of various aspects of transplantation (78) and pathologic (79) and immunologic changes (80) in different liver diseases. An important goal of the Division of Liver Disease is making transplantation unnecessary by curing and ultimately preventing liver diseases.

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17

Alcohol and the Liver:

Metabolism of Alcohol and Its Role in Hepatic and Extrahepatic Diseases

Charles S. Lieber, M.D.

Abstract

Dr. Charles S. Lieber has conducted clinical and experimental studies for more than four decades (three at Mount Sinai and the Bronx VA Medical Centers) with emphasis on liver, nutrition and GI pathophysiology. His major contributions include elucidation of the pathogenesis of alcoholic liver disease, by demonstrating the toxic role of alcohol and describing associated metabolic disorders. This was achieved through judicious clinical studies and newly developed rodent and primate models with the administration of ethanol in liquid diets. The mechanisms of various pathological and metabolic effects of ethanol were clarified, including hyperlipemia (with the rise in HDL), hyperuricemia, the role of acetaldehyde toxicity and alcohol-induced oxidative stress. The latter, including glutathione depletion, was corrected by S-adenosyl-1-methionine given to alcohol-fed baboons; the compound is now being used successfully for the treatment of patients with alcoholic liver disease in Europe. Alcoholic cirrhosis was produced for the first time in nonhuman primates and shown to be fully prevented by polyenylphosphatidylcholine, which is now being tested in a multicenter clinical trial. Lieber also discovered a new (microsomal) pathway of ethanol metabolism, responsible for the tolerance to ethanol and for several clinically important toxic interactions with other drugs (e.g., acetaminophen), anesthetics, industrial solvents, carcinogens, as well as retinol and β-carotene, with narrowing of their therapeutic window. His work defined the role of the stomach in ethanol metabolism, description of corresponding gender differences, cloning (for the first time) of the gene for sigma ADH (a newly recognized gastric alcohol dehydrogenase isozyme) with its chromosomal localization, and the discovery of the effects of commonly used medications (e.g., H_2 blockers and aspirin) on the activities of the enzyme and on blood alcohol levels in social drinkers. Lieber was among the first to use antibiotics for the elimination of gastric bacterial urease and its ammonia production in man, thereby alleviating chronic gastritis and hypoacidity, with attenuation of hepatic encephalopathy in cirrhotics. He promoted early detection and treatment of heavy drinkers before their social or medical disintegration, by defining precirrhotic lesions and markers of alcohol consumption.

Conclusions: The research of Dr. Lieber and his group has yielded a better understanding of the pathogenesis of common hepatic, gastric and nutritional disorders, with elucidation and prevention of serious toxic alcohol-drug interactions and the development of methods for early recognition and more effective approaches to prevent and treat liver and gastrointestinal diseases.

Key Words: Ethanol, liver, cirrhosis, drugs, nutrition.

A. Alcohol and Nutrition

Ethanol is a psychoactive drug, but, besides its pharmacologic action, it has a substantial energy value (7.1 kcal/g). In the heavy drinker, alcohol represents, on the average, 50% of the total dietary energy intake. As a consequence, alcohol displaces many normal nutrients of the diet, resulting in primary malnutrition and associated symptomatology (Fig. 1). Alcohol also impairs the activation and utilization of nutrients, and secondary malnutrition may result from either maldigestion or malabsorption caused by gastrointestinal complications associated with alcoholism. Originally, it was believed that liver disease in the alcoholic was due exclusively to malnutrition. This dogma was primarily based on the experiments of Best and Hartroft, who had observed that in rats given alcohol as part of their liquid diet, no liver damage resulted when the diet was adequate. The first stage of liver disease, namely fatty liver, only developed when the diet was deficient. From their experiments, Best et al. (1) concluded that "there is no more evidence of a specific toxic effect of pure ethyl alcohol upon

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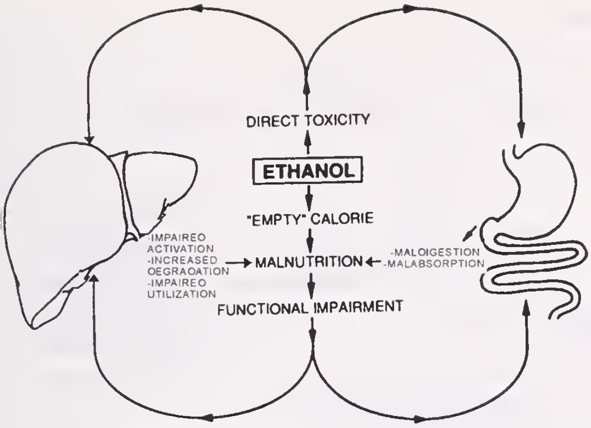

Fig. 1. Interaction of direct toxicity of ethanol on liver and gut with malnutrition secondary to dietary deficiencies, maldigestion, and malabsorption, as well as impaired hepatic activation or increased degradation of nutrients (154).

liver cells than there is for one due to sugar." Lieber et al. confirmed these experiments but added the observation that under those conditions, blood alcohol levels were negligible. Indeed, rats have a natural aversion for alcohol that was overcome by giving alcohol in totally liquid diets (2). This diet also allowed perfect pair feeding of controls and, using such a diet, it was established for the first time that alcohol, even in the absence of nutritional deficiencies, can cause the first stage of alcoholic liver disease, namely a fatty liver, a finding confirmed in human volunteers (2, 3). The question still remained of the pathogenesis of the more severe stages of alcoholic liver disease, culminating in cirrhosis, which is responsible for the high rate of mortality in the heavy drinker. This issue was addressed by extending the liquid diet technique to an experimental animal more closely related to man, namely nonhuman primates (4). The latter studies were conducted after Dr. Lieber and his team had moved from Harvard and Cornell to the Bronx Veterans Affairs (VA) Medical Center and the newly created Mount Sinai School of Medicine in 1968. There, it was shown for the first time that alcohol can cause cirrhosis of the liver, even in the absence of nutritional deficiencies (4, 5).

This realization had profound consequences on the preventive as well as therapeutic approaches to the medical disorders of alcoholism. The major therapeutic efforts shifted from the mere correction of nutritional deficiencies to the moderation of alcohol consumption and the development of new therapeutic modalities by a better understanding of the mechanism of hepatotoxicity. The latter was investigated by a systematic study of the biochemical pathways through which the body rids itself of the alcohol.

B. Alcohol Metabolism and Associated Toxicity

Alcohol is oxidized primarily in the liver and the main pathway involves alcohol dehydrogenase.

1. *Metabolic Disorders Associated with Alcohol Oxidation by Alcohol Dehydrogenase*

a. Hepatic effects

The oxidation of ethanol via the alcohol dehydrogenase pathway results in the production of acetaldehyde with loss of H. Nicotinamide adenine dinucleotide (NAD) is reduced to NADH. The large amounts of reducing equivalents generated overwhelm the hepatocyte's ability to maintain redox homeostasis, and it was shown that a number of metabolic disorders ensue (Fig. 2), including hyperuricemia (6) and hyperlipemia (2), with a rise in HDL (7) popularized more recently in conjunction with some apparently beneficial effects of moderate drinking on coronary arteries. It was also found that the increased NADH opposes lipid oxidation and promotes fatty acid synthesis with, as a net result, hepatic fat accumulation (8). The perivenular exaggeration of this redox change (because of the relative perivenular hypoxia) was found to be responsible for the exacerbation of the alcohol-induced injury (including steatosis) in the perivenular zone of the hepatic lobule (9). The respective roles of the amount of dietary fat (10) and dietary deficiencies (11) were elucidated. An associated metabolic disorder, namely ketoacidosis, was discovered and defined (12). In addition to the raised NADH, microsomal induction (*vide infra*) was incriminated through increased activity of enzymes involved in lipogenesis (13, 14) which was found to be associated with enhanced production of low and very low density lipoproteins (LDL and VLDL) (15). LDL and VLDL, in addition to alterations in cholesterol turnover (16), were shown to play a role in the alcohol-induced hyperlipemia (17–19). The latter was observed to involve the high density lipoproteins (HDL). Their increase was described by Baraona and Lieber (7), and has gained much attention in recent years. Ethanol was also found to affect the lipids, the microviscosity (20) and the structure of plasma membranes, as demonstrated by scanning electron microscopy (21). Thus, the hypothesis that the NADH generated by alcohol dehydrogenase (ADH)-mediated ethanol oxidation may play a major role in alcohol-induced disorders (22) was shown indeed to explain a vast array of associated metabolic abnormalities, including the steatosis (Fig. 2).

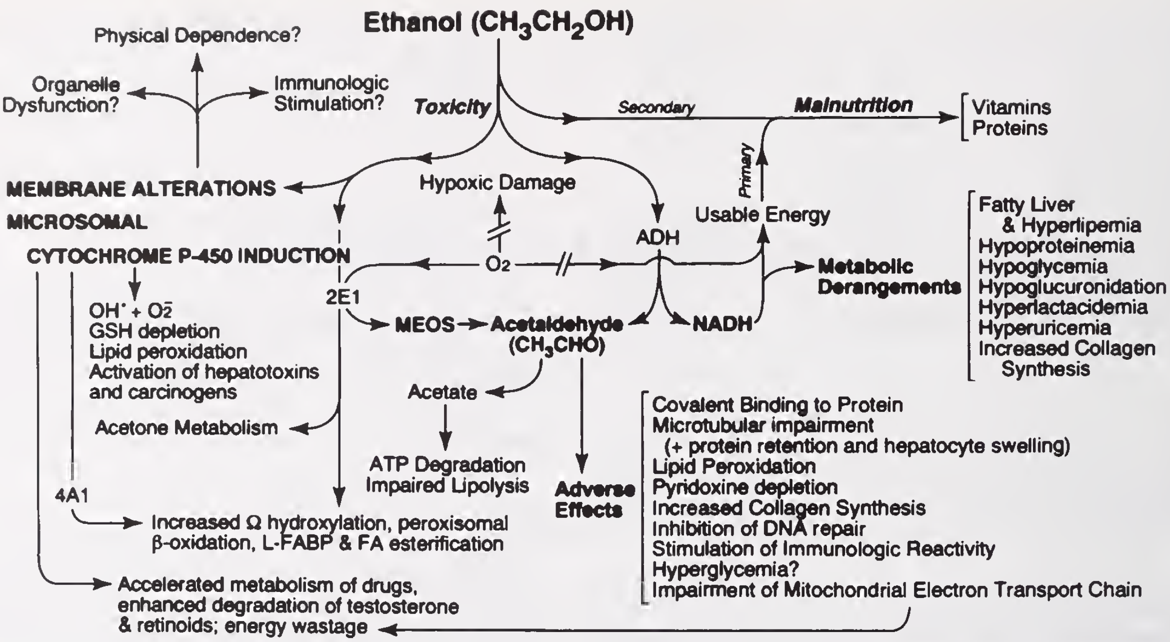
Ethanol (CH_3CH_2OH)
Physical Dependence?
Organelle Dysfunction?
Immunologic Stimulation?
Toxicity
Secondary
Malnutrition
Vitamins
Proteins
Primary
MEMBRANE ALTERATIONS
MICROSOMAL
CYTOCHROME P-450 INDUCTION
Hypoxic Damage
ADH
Usable Energy
O_2
2E1
MEOS
Acetaldehyde (CH_3CHO)
NADH
Metabolic Derangements
Fatty Liver & Hyperlipemia
Hypoproteinemia
Hypoglycemia
Hypoglucuronidation
Hyperlactacidemia
Hyperuricemia
Increased Collagen Synthesis
OH˙ + O_2^-
GSH depletion
Lipid peroxidation
Activation of hepatotoxins and carcinogens
Acetone Metabolism
Acetate
ATP Degradation
Impaired Lipolysis
Adverse Effects
Covalent Binding to Protein
Microtubular impairment
(+ protein retention and hepatocyte swelling)
Lipid Peroxidation
Pyridoxine depletion
Increased Collagen Synthesis
Inhibition of DNA repair
Stimulation of Immunologic Reactivity
Hyperglycemia?
Impairment of Mitochondrial Electron Transport Chain
4A1
Increased Ω hydroxylation, peroxisomal β-oxidation, L-FABP & FA esterification
Accelerated metabolism of drugs, enhanced degradation of testosterone & retinoids; energy wastage

Fig. 2. Hepatic, nutritional and metabolic abnormalities after ethanol abuse. Malnutrition, whether primary or secondary, can be differentiated from metabolic changes or direct toxicity, resulting partly from redox changes, or effects secondary to microsomal induction, including increased acetaldehyde production (155).

b. Gastric effects

1. Gastric ethanol metabolism and interactions with other drugs

Chronic ethanol consumption was found to produce a significant decrease in gastric alcohol dehydrogenase (ADH) activities (23), associated with greater bioavailability (lesser first pass metabolism) of ethanol (23, 24). Significant ethanol metabolism was also observed in cultured rat (25) and human (26) gastric cells. Women were found to have a lower gastric ethanol metabolism than men, which explains, at least in part, their greater susceptibility to the effects of ethanol (27). Commonly used drugs, e.g., aspirin (28) and H_2 receptor antagonists, e.g., cimetidine (29), were discovered to inhibit gastric ADH activity and to enhance the bioavailability of ethanol, with a resulting increase in blood ethanol levels (30). This effect was shown to be particularly important for social drinkers who commonly take several small drinks, with a cumulative effect on blood alcohol levels, strikingly exaggerated by various drugs (Fig. 3), either because of an inhibition of gastric ADH (*vide supra*) and/or an acceleration of gastric emptying (31).

At least three different forms of ADH were observed in the human stomach, with either high or low K_m's for ethanol (32), including a newly recognized gastric isozyme, now called class IV or sigma ADH. A deficiency of this gastric ADH was uncovered in Asians (33), and the lower ADH activity was found to be associated with a lesser first pass metabolism of ethanol (34), in keeping with a predominant role for ADH in human first pass metabolism. The full length cDNA of sigma ADH was determined and the complete amino acid sequence deduced (35). The corresponding ADH_7 gene in Caucasian and Japanese subjects was compared (36), including the upstream structure and the organ distribution of its expression (37) with, for the first time, molecular cloning and chromosomal localization of the gene (38). These studies not only established

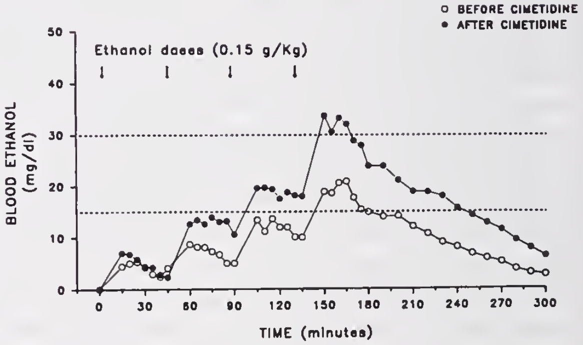

Fig. 3. Effects of cimetidine (400 mg twice a day for 7 days) on average blood levels after oral consumption of ethanol in nine subjects. Four small doses of ethanol (150 mg/kg) were imbibed at 45-min intervals, before and after administration of cimetidine. The effect of cimetidine on repeated drinking was significant ($p < 0.01$ by two-way analysis of variance for repeated measures). (Modified from ref. 156).

the role of gastric ADH in ethanol metabolism, but they also delineated corresponding differences at a molecular level and opened a new approach to explain differences in the handling of ethanol and possibly of other dietary xenobiotics, such as gastric carcinogens.

2. Gastritis in the alcoholic

The product of ethanol metabolism is acetaldehyde, a toxic compound (*vide infra*) which may contribute to the chronic gastritis which is common in the alcoholic. An additional pathogenic factor is *Helicobacter pylori* infection (HP). Indeed it was found that this chronic gastritis generally resolves with the eradication of the microbe (39). The role of the gastric microbial flora in converting urea into NH_3 was first recognized by the successful elimination of gastric NH_3 using antibiotics in man (40, 41). These studies were completed at Mount Sinai (42). Adverse effects of NH_3 included hypoacidity and gastritis, especially in the alcoholic (41). Gastric NH_3 was shown to correlate with the severity of gastritis (39), and its measurement is now the basis for an accurate, yet simple, method for the detection of HP (43). The infection has its most striking impact in patients with uremia (40, 41) and in those with cirrhosis whose encephalopathy was improved with the antibiotic therapy (44).

Other gastrointestinal effects of ethanol that were elucidated comprised significant intestinal lesions in the rat (45), confirmed in man (46). These alterations included B_{12} malabsorption (47) and decrease of intestinal lactase (46).

2. *Microsomal Ethanol Oxidizing System (MEOS)*

a. Ethanol metabolism

A toxicological breakthrough was achieved with the discovery of a microsomal ethanol oxidizing system and its interactions with xenobiotics (48, 49). This second pathway for alcohol metabolism was separate from that of alcohol dehydrogenase and catalase (49, 50) and characterized (51) and reconstituted by a semi-purified preparation of cytochrome P-450 (52). The role of the microsomes in ethanol metabolism and its increase after chronic ethanol consumption was demonstrated in rats (53), nonhuman primates (54, 55), acatalasemic mice (56), and deermice lacking alcohol dehydrogenase (57–62). It was quantitated using, in part, deuterium isotope effects (61). An ethanol-inducible form of cytochrome P-450 was discovered (52) and was subsequently purified by various groups from the livers of different species, including rats (63) and humans (64); it is now called 2E1. Unlike ADH, MEOS was found to be strikingly inducible by chronic ethanol consumption, with its key component, namely 2E1, increased 4- to 10-fold in liver biopsies of recently drinking subjects (65), with a corresponding rise in mRNA in hamsters (66), rats (67) and man (68). P4502E1 induction was demonstrated with normal, as well as low-fat diets (69). It was shown in hepatocytes and in nonparenchymal cells of the liver (70), and also in extrahepatic tissues (71).

b. Other microsomal effects

Microsomal induction was found to have an impact on sex hormones in normal men (72), and to enhance fatty acid ω-oxidation (73). Induction of 2E1 contributes to the tolerance that develops to ethanol in the alcoholic and other drugs that are microsomal substrates. The tolerance of the alcoholic to various psychoactive drugs had generally been attributed to central nervous system adaptation, but metabolic adaptation now had to be considered, because the clearance rate of many drugs from the blood was found to be enhanced in alcoholics (74). Indeed, controlled studies have shown that chronic administration of pure ethanol with nondeficient diets either to rats or man (under metabolic ward conditions) results in a striking increase in the rate of blood clearance of ethanol (75), meprobamate and pentobarbital (74) as well as other drugs.

Contrasting the effect of chronic ethanol consumption, which results in microsomal induction and tolerance to a number of drugs, the presence of ethanol may slow down disposition of some drugs and enhance their pharmacologic effects by competing for some common component(s) of the microsomal degradation process. This was shown for meprobamate (76), acetaminophen (77, 78) as well as methadone (79).

c. Activation of hepatotoxins

One of the most important consequences of the discovery of this new microsomal pathway of ethanol metabolism was the realization that the ethanol-inducible cytochrome P4502E1 not only catalyzes ethanol oxidation, but is also capable of activating various other compounds to highly toxic metabolites. This pertains to analgesics, such as acetaminophen (80), anesthetics (81), hepatotoxins (82), industrial solvents (83), as well as carcinogens (e.g., nitrosodimethylamine [NDMA]) (84). Activation of the latter was achieved at concentrations significantly lower than those required after the administration of other inducers (84), in part because the ethanol-inducible P4502E1, including the human variety (64), has a high affinity for NDMA. Increased activation of carcinogens was also demonstrated in the alimentary tract and the lungs (85). Thus, this inducible microsomal ethanol oxidizing system explains not only the metabolic tolerance to ethanol that develops in the heavy drinker, but also the concomitant increased vulnerability to ubiquitous xenobiotics. Furthermore, the proliferation of the endoplasmic reticulum (86) associated with P4502E1 induction is also accompanied by enhanced activity of other cytochrome P-450s, resulting in accelerated metabolism and tolerance to other drugs, as well as increased degradation of retinol and its hepatic depletion.

d. Interactions with retinoids and carotenoids

Liver microsomes were also found to harbor hitherto unrecognized pathways for retinol metabolism (87, 88) which were found to play a role in the homeostatic control of hepatic vitamin A levels (89). Using purified cytochrome P-450 isozymes, including the human P4502C8 (90), retinol (87, 90) and retinoic acid (90, 91), metabolizing systems were reconstituted; chronic ethanol or drug administration was shown to result in increased microsomal degradation of retinoic acid (92) and retinol (93). This provided a possible mechanism for the striking hepatic vitamin A depletion which was discovered to result from chronic ethanol consumption in rats (94), nonhuman primates (94), and man (95) (Fig. 4). This hepatic vitamin A depletion was associated with striking lysosomal lesions (96). Potentiation of the deleterious effects of vitamin A depletion by ethanol was also found in other tissues, including a profound loss of the ciliated epithelium in the lining of the respiratory tract and the exacerbation of squamous metaplasia, a precancerous lesion (97). Hepatic depletion of vitamin A was also demonstrated after administration of other drugs (98); the combination of ethanol with drugs or food additives (such as butylated hydroxytoluene) resulted in a striking potentiation of the depletion, with almost all of the vitamin A disappearing from the liver (99).

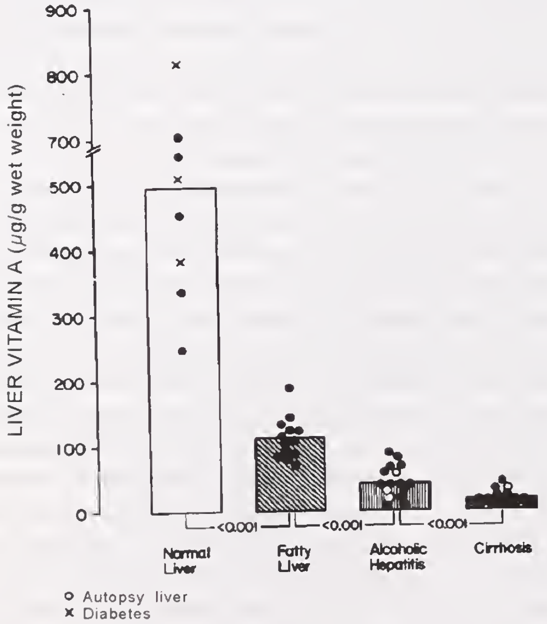

Fig. 4. Hepatic vitamin A levels in subjects with normal livers and various stages of alcoholic liver injury. Figures below the graph denote P values (95).

Thus, vitamin A requirements had to be revised for the large segment of our population that chronically abuses ethanol and/or other drugs. The practical limits of vitamin A supplementation, however, were delineated by the demonstration that vitamin A toxicity can be markedly exacerbated by chronic ethanol consumption, with development of mitochondrial injury (100), necrosis and fibrosis (101). Indeed, amounts of ethanol and vitamin A which, by themselves, did not produce fibrosis, when combined, resulted in necrosis and fibrosis in the liver (101), with development of severe mitochondrial injury (100). Furthermore, it was discovered that alcohol interferes with the clearance of β-carotene, possibly by impairing its conversion to vitamin A, resulting in enhanced hepatic and blood levels in baboons (102) and also in man (103), with associated potentiation of hepatotoxicity (102) possibly due, in part, to the beadlets used as carrier for β-carotene (104). In addition, carotenoids were found to undergo significant biliary excretion in man (105) and are therefore affected by liver pathology. The recognition of a narrowed therapeutic window for vitamin A and β-carotene in the alcoholic has prompted a redefinition of the optimal conditions for their use in nutritional repletion and therapy.

C. Acetaldehyde Toxicity and Mitochondrial Impairment

Ethanol oxidation, whether by the ADH or the microsomal pathway, results in acetaldehyde, which may cause ubiquitous damage, including in the mitochondria. Indeed, the ethanol-induced ultrastructural lesions of the mitochondria (86) were found to be associated with functional abnormalities, including decreased oxidation of fatty acids (106) and acetaldehyde (107, 108). The latter, together with the increased production by the induced microsomes (109), explains the elevated blood level of acetaldehyde observed in alcoholics (110). Using improved analytical methods (111), the high acetaldehyde levels were found to be reversible upon alcohol withdrawal

(112), and exaggerated by pregnancy and lactation (113). The human placenta was shown to be capable both of transferring acetaldehyde from the mother to the fetus and of converting ethanol to acetaldehyde (114), which may thus play a role in the pathogenesis of the fetal alcohol syndrome, the most common preventable cause of congenital abnormalities.

Administration of ethanol, particularly at high levels and in animals fed alcohol chronically, was accompanied by a 10-fold increase in splanchnic acetaldehyde release in the hepatic vein (115), associated with a striking leakage of the mitochondrial enzyme glutamic dehydrogenase into the hepatic venous blood. There was also an inappropriately low oxygen utilization by the liver. The flow-independent O_2 extraction (VO_2) was measured by reflectance spectroscopy with a probe placed on the liver surface through a peritoneoscope: VO_2 significantly decreased after the high ethanol dose in the alcohol-treated baboons (115). This impaired O_2 utilization was associated with a marked shift in the mitochondrial redox level (measured by the β-hydroxybutyrate / acetoacetate ratio). A "vicious cycle" was thus recognized, with chronic ethanol consumption inducing increased acetaldehyde formation leading to mitochondrial toxicity, including an associated decreased capacity of the mitochondria to oxidize acetaldehyde. As a consequence, acetaldehyde rises even further, and perpetuates and aggravates the toxicity.

The morphologic (116) and functional (117) impairment of the mitochondria after chronic ethanol consumption was accompanied by a significant decrease in cytochrome oxidase activity associated with the depletion of mitochondrial phosphatidylcholine, whereas restoration of cytochrome oxidative activity was achieved by replenishment of the phosphatidylcholine *in vitro* (117). This observation was one of the factors that led to the supplementation of phosphatidylcholine *in vivo* (using delinoleoylphosphatidylcholine), which resulted in the discovery of its spectacular beneficial effects, including the prevention of liver fibrosis and cirrhosis (*vide infra*). The uncoupling of oxidation with phosphorylation associated with mitochondrial impairment, together with the net loss of chemical energy that accompanies the operation of the induced microsomes explained, at least in part, the startling observation that "alcohol calories do not fully count" and why many alcoholics do not maintain an adequate body weight despite a large caloric intake (118).

One mechanism for the hepatotoxicity of acetaldehyde is its high chemical reactivity and formation of adducts with various proteins. Indeed, it was discovered that acetaldehyde binds to microsomal proteins (119) and forms adducts *in vivo* with P4502E1 (120), collagen (121 – 122), as well as VLDL and LDL (123). Acetaldehyde adducts also elicit an immune response with increased circulating antibodies in alcoholics (124). The appearance of antibodies against acetaldehyde-protein adducts was found to reflect the severity of liver disease, both in alcoholics and non-alcoholics (125). Furthermore, even in non-alcoholic liver disease, hepatic acetaldehyde was found to be increased to a potentially toxic level (126). Moreover, acetaldehyde toxicity was shown to interfere with the repair of alkylated nucleo-proteins; human and rat O6 methylguanine transferase was inhibited *in vitro* by minute concentrations of acetaldehyde (as low as 0.01μM) (127). Acetaldehyde binding was also shown to impair microtubule polymerization and hepatic protein secretion (128, 129) which, together with an increase in constituent proteins (130), resulted in protein accumulation and hepatocyte swelling, thereby explaining the ballooning of the hepatocyte and the hepatomegaly, two characteristic features of alcohol-induced liver injury.

Acetaldehyde also contributes to depletion of glutathione and its potentiation of lipid peroxidation (131), verified in human liver biopsies (132). These effects were found to be attenuated by S-adenosyl-L-methionine (133), which has now been introduced in Europe for the treatment of liver disease. The oxidative stress was exacerbated by a low vitamin E diet, and ethanol was found to aggravate hepatic vitamin E depletion, in part by promoting conversion of α tocopherol to α tocopheryl-quinone (134), probably by free radical reaction. Allopurinol partially prevented the ethanol-induced lipid peroxidation (135), most likely through inhibition of purine degradation (enhanced by ethanol) and the associated free radical generation.

D. Fibrosis and Cirrhosis of the Liver: Pathogenesis and Prevention

Traditionally, fibrosis and cirrhosis were viewed as a "scarring" response to the necrosis and inflammation associated with liver injury, most clearly demonstrated in alcoholic hepatitis. However, the observation that chronic alcohol administration (under controlled dietary conditions) stimulated fibrogenesis (136) and produced cirrhosis in the baboon (4) without an obvious stage of alcoholic hepatitis (137) but with evidence for increased collagen production, including enhanced type I procollagen mRNA (138), raised the hypothesis of a more direct effect of alcohol on fibrogenesis. Indeed, in baboons fed alcohol (139) as well as in man (140), perivenular fibrosis was identified as a precirrhotic lesion and shown to be useful for the early detection of subjects prone to rapidly develop cirrhosis, even in the absence of alcoholic hepatitis (141) (Fig. 5). Scanning electron microscopy also revealed significant changes of the endothelial fenestrations of the liver sinusoids (142), a finding of obvious implications for the exchange of nutrients and metabolites between the hepatocytes and the blood. Efforts were then directed to define the cell(s) involved. Myofibroblasts were identified in normal liver (139) and were discovered to proliferate after chronic alcohol consumption (139, 140). Furthermore, stellate cells (also called lipocytes or fat-storing cells) were found to be transformed or activated to “transitional” myofibroblast-like cells (143), associated with active fibrogenesis. Lipocytes and myofibroblasts were isolated from the liver and cultured, and acetaldehyde was shown to stimulate collagen production *in vitro* (144, 145), with an associated increase in mRNA for collagen (146). The acetaldehyde-induced increase in collagen accumulation was prevented by polyunsaturated phosphatidylcholine (PPC) extracted from soybeans (147) and by its main phosphatidylcholine species, namely dilinoleophosphatidylcholine (DLPC) (148), selected because of its high bioavailability. Several modes of action were elucidated: increased collagen breakdown (148), a significant decrease in the number of lipocytes activated to myofibroblast-like cells (148, 149), correction of the ethanol-induced depletion in phosphatidylcholine (148), as well as an attenuation of some of the associated enzyme deficiencies, including that of phosphatidylethanolamine methyltransferase (150). More recently, PPC was also found to prevent alcohol-induced steatosis and hyperlipemia (151) and to exert an unexpected but potent antioxidant effect (152) of possible relevance to the fibrosis, since the latter is known to be stimulated by products of lipid peroxidation. Furthermore, PPC prevented or attenuated nonalcoholic cirrhosis produced by either CCl_4 or heterologous albumin in the rat and accelerated the regression of preexisting cirrhosis (153). PPC is now being tested in man.

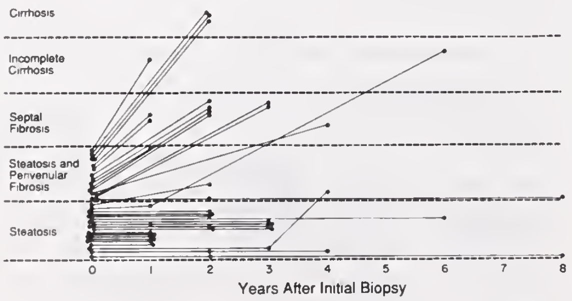

Fig. 5. Progression of fibrosis in alcoholics without hepatitis followed up to eight years after initial biopsy. The presence of perivenular fibrosis on the initial biopsy specimen was found to be a harbinger of rapid development of fibrosis to more severe stages, including cirrhosis (141).

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Erratum

We regret an error in the article by J.L. Werther entitled "The Gastric Mucosal Barrier" which appeared in v67, No. 1, January 2000 on page 43, right column, 15 lines from the bottom. The word "administered" should be replaced by "administration."

Grand Rounds

Fecal Incontinence:

A Clinical Approach

Zara R. Cooper, B.S.[1], and Suzanne Rose, M.D., M.S.Ed.[2]

Abstract

"Fecal incontinence" is defined as the involuntary loss of stool at any time of life after toilet training. It is a socially and psychologically devastating condition for patients and their families, and a topic which both patients and physicians are reluctant to approach. Although the true prevalence of fecal incontinence is unknown, studies have reported it to be as high as 2.2% in the general population, with significantly higher rates among nursing home residents and hospitalized elderly. Risk factors include advancing age, female gender and multiparity.

An understanding of pelvic floor anatomy and physiology is required to appreciate how diverse medical conditions can affect mechanisms involved in normal continence. The rectum serves as a storage reservoir until elimination can take place at a socially acceptable time and place. The pelvic floor muscles help to regulate the defecatory process and maintain continence. These muscles include the internal anal sphincter, the external anal sphincter and the puborectalis muscle. Each muscle contributes to normal continence, although the relative importance of each is controversial. Neurologic integrity and sensation are also key factors.

Conditions associated with fecal incontinence include diarrheal states, fecal impaction, idiopathic neurologic injury, surgical and obstetric injury, pelvic trauma, collagen vascular disease, and neurologic impairment related to stroke, diabetes, or multiple sclerosis. Evaluation of the patient with fecal incontinence includes a directed history and physical examination, with particular attention paid to integrity of the perineum and rectum, and a complete neurologic evaluation. Diagnostic tools such as stool studies, anorectal manometry, defecography, electromyography, pudendal nerve conduction, and endoanal ultrasound may be employed in an outpatient setting. Fecal incontinence may be treated conservatively by employing such methods as dietary restriction, stool bulking agents, and biofeedback. Surgery may be the best option for cases refractory to medical treatment, or for those patients with rectocele or obstetrical injury.

In this article, we review the presentation, epidemiology, pathophysiology, and etiology of fecal incontinence. Evaluation, including key components of directed history and physical examination, and the appropriate use of diagnostic studies and indications for treatment options are also addressed. **Key Words:** Fecal incontinence, functional bowel disorder, anorectal disorders, anorectal physiology.

Introduction and Epidemiology

Fecal incontinence is defined as the involuntary loss of stool at any time of life after toilet training. It is a devastating condition for patients and their caretakers, and a topic which physicians and patients are reluctant to discuss. The exact prevalence of fecal incontinence in the population is unknown. Current data suggest that the occurrence may be much greater than is generally thought. One survey found that almost 14% of adult patients visiting their primary care physician had experienced fecal incontinence, and that 10.5% of those had restricted their activity due to the condition (1). It is notable that only one-fifth of the affected patients had discussed the topic with their physicians. A community-based study of Wisconsin residents found that 2.2% of the general population had anal incontinence of gas, liquid or feces (2). Of these subjects, 30% were older than 65 and 63% were women. The same study found that independent risk factors for incontinence included advancing age, female sex, poor general health and physical limitations. Other reports have estimated that 10–17% of nursing home residents (3, 4) and between 13 and 47% of hospitalized elderly (5, 6) have some incontinence. In fact, it is the second most common cause for institutionalizing the elderly (7).

---

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Adapted from a Grand Rounds presentation to the Department of Medicine, Mount Sinai School of Medicine, New York, NY on March 9, 1999.

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Double incontinence of urine and feces is 12 times more common in geriatric patients than fecal incontinence alone (4). Women of all ages are disproportionately affected by this condition. The incidence is eight times higher in 45-year-old women than in men of the same age (8). The costs of this disorder are unknown. However, the recent explosion of the adult diaper market is indicative of its economic importance.

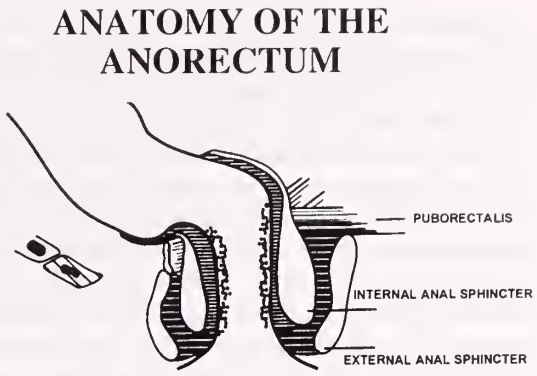

Fig. 1. Anatomy of the rectum.

Anatomy and Physiology of Normal Continence

An understanding of pelvic floor anatomy and physiology is key to appreciating the etiology and treatment of fecal incontinence and disorders of the pelvic floor (Table 1). The pelvic floor muscles help to regulate the defecatory process and maintain continence. The rectum serves as a storage reservoir until elimination can take place at a socially acceptable time and place. The muscles of the pelvic floor include the internal anal sphincter, the external anal sphincter and the puborectalis muscle (Fig. 1). Each muscle contributes to normal continence, although the relative importance of each is controversial.

The internal anal sphincter (IAS) is continuous with the smooth muscle layer of the rectum, and is under the control of the enteric nervous system. The IAS is tonically contracted and generates 80% of the anorectal resting pressure to prevent involuntary defecation (9, 10). The sphincter relaxes during defecation, in response to stretch by as little as 20–40 mL of rectal contents; this relaxation is caused by the rectoanal inhibitory reflex (RAIR) (11). This sphincter is under autonomic control by sympathetic innervation from the hypogastric plexus, which initiates tonic contraction, and by sacral parasympathetic fibers, which in turn mediate rectoanal muscle relaxation. Dysfunction of the internal anal sphincter muscle leads to a transient increase in intraluminal pressure, followed by a decrease in pressure. These dynamic changes are mediated by the rectoanal inhibitory reflex via parasympathetic nerves. In the absence of neuropathy, nerve endings in the anal canal can differentiate between solid, liquid and gas in the rectum via what is known as the sampling reflex.

TABLE 1
Factors Required for Normal Continence

Normal sphincter function
Neurologic integrity
Rectal sensation
Normal stool volume and consistency
Normal colonic transit time
Rectal storage capacity
Psychological motivation

The external anal sphincter (EAS) is a striated muscle under voluntary control, which contributes up to 20% of the resting pressure in the anal canal (9, 12). This muscle is innervated by the pudendal nerves (S2, S3, S4). Controversy exists as to whether the EAS is a single muscle or a triple-loop system consisting of deep, superficial and subcutaneous loops, each with its own innervation (13). It is partially contracted at rest, and undergoes tonic contraction approximately every fifteen minutes by reverse peristalsis (11). Inhibition of the EAS during defecation allows for the passage of stool. A spinal reflex stimulates contraction (14) of the EAS whenever external pressures increase, such as with erect posture and coughing (15, 16). It should be noted that external pressures decrease during sleep (17). Tactile stimulation of the perianal skin will elicit phasic contraction of the EAS, commonly referred to as the "anal wink," via the anocutaneous reflex.

The puborectalis muscle (PRM) seems to be most directly responsible for continence (11, 18). The PRM is also innervated by the pudendal nerve, and remains partially contracted at rest. It forms a U-shaped sling around the anorectal junction and connects to the bony pelvis. The PRM maintains a 92-degree angle (19) between the rectum and the anal canal, which obstructs the outlet and prevents the passage of solid stool. Voluntary contractions further narrow the anorectal angle. During normal defecation, relaxation of the PRM and descent of the pelvic floor widen this angle to approximately 135 degrees. Idiopathic fecal incontinence, spinal cord injuries and descending perineum syndrome are accompanied by a more obtuse angle. Other factors related to normal continence include stool volume and consistency, stool transit time, neurologic integrity and rectal sensation, rectal storage capacity, and psychological motivation.

In normal subjects, the resting rectal pressures exceed pressures in the sigmoid colon, resulting in a retrograde pressure gradient which prevents the contents of the sigmoid from entering the rectum too quickly. Rectal incontinence may result from disruption of this pressure differential between the sigmoid and the rectum when colonic transit is so fast that the reservoir capacity of the rectum is overwhelmed. Anorectal pressures are determined by extrinsic pressures such as increased intra-abdominal pressure and intrinsic pressures generated by the bowel wall and muscles of the pelvic floor (2). A high-pressure zone is generated by the tonic contraction of the IAS, EAS, and PRM (20), preventing passage of stool from the sigmoid to the rectum and also preventing emptying of the rectum (21).

Incontinence

Factors associated with fecal incontinence are listed in Table 2. Major incontinence is characterized by frequent and regular inability to control stool of any consistency. It is most often due to surgical and other trauma, or pelvic floor neuropathy (8) (Table 3). Incontinence is considered to be minor when the patient is unable to control passage of flatus or loose stool and this results in soiling of the undergarments. This is most often due to some surgical injury to the IAS or to overflow incontinence.

The rectum has both viscous and elastic properties that allow it to maintain low intraluminal pressure, even if the volume is large (22). Changes in compliance can affect continence. If compliance is decreased, smaller volumes of stool can cause increased pressure and impair rectal storage function. Incontinence accompanied by urgency and frequency may result. Conditions that may decrease compliance include inflammatory disease (23), radiation injury (24), and coloanal anastomosis. An anatomic obstruction, such as may occur with a fecal impaction, may result in overflow incontinence whenever liquid stool circumvents the offending obstruction. This situation may be associated with increased compliance.

TABLE 2
Factors Associated with Fecal Incontinence

- Gender
- Age
- Abnormal rectal compliance
  - increased compliance
    - megarectum
    - fecal impaction
  - decreased compliance
    - inflammatory bowel disease (IBD)
    - radiation proctitis
    - coloanal anastomosis
- Diarrhea
- Sphincter insult
  - trauma, surgery
- Neuropathy
- Prolapse

In rare instances, profuse diarrhea can cause incontinence even in the presence of normal pelvic floor and sphincter mechanisms. Rapid colonic transit time and increased volume can overwhelm rectal storage capacity. Furthermore, diarrhea will stress normal continence mechanisms since it is more difficult to perceive and retain liquid stool than solid.

Impaired proprioception in the levators, puborectalis, and sphincters will decrease a patient's ability to sense rectal filling and cause loss of the normal warning that defecation is imminent (25). In mentally ill or geriatric patients, megarectum resulting in fecal impaction is often associated with decreased sensation. Intact autonomic pathways will still cause the IAS to relax in response to a fecal bolus. Consequently, the IAS will relax before the patient perceives rectal stretch (7). The result is fecal impaction and overflow incontinence (26), of which the patient may be unaware (11).

TABLE 3
Anorectal Abnormalities in Fecal Incontinence

Patient Categories	Reservoir	Sphincters	PRM	Sensation
Anal trauma	N	A	N	N
Idiopathic	N	A	A	N
Diabetes	N	A	?	A
Proctitis	A	N	N	N
Neurogenic	N	A	A	A

N = normal
A = abnormal

The effort to delay defecation initially requires powerful initiation of contraction of the EAS, which increases pressure within the anal canal. To prolong the delay, contraction must be sustained. One limited study by Read and Read (27) found the mean duration of contraction to be 3.2 minutes; others report mean time of 1 – 3 minutes for the EAS to fatigue completely (28). The inability to sustain a contraction (the fatigue phenomenon) is often more disabling to patients with incontinence than the inability to generate a peak effort. Marcello et al. (29) developed the fatigue rate index (FRI) to evaluate the fatigue rate of the EAS. They found that the FRI was approximately 2 minutes longer in controls than in incontinent subjects.

Anal trauma or surgery may cause incontinence, due to myopathic or neuropathic sphincter injury. Neurologic impairment caused by bilateral sacral denervation is also associated with diabetic autonomic neuropathy and neurologic disorders such as multiple sclerosis and meningomyelocele. Insult to the sphincter of the EAS and IAS does not necessarily cause incontinence. However, decreased IAS tone can impair resting pressures and lower the threshold for the sampling reflex which distinguishes solid from liquid and gas (30).

Idiopathic denervation of the PRM or EAS can also impair the sampling reflex, leading to sensory incontinence. The patient may know that he or she is passing contents, but be unable to prevent an accident. Idiopathic incontinence is most common in multiparous middle-aged or elderly women, and may be due to traction injuries (14) secondary to vaginal delivery (30) or excessive pelvic floor descent during defecation over a long period of time (31). Many patients have perineal descent and widening of the anorectal angle consistent with weakening of the striated muscles of the pelvic floor. It has been suggested that women are more susceptible to this type of injury because the morphology of the pelvic floor muscles may be hormone-dependent (32).

Age is also a known risk factor for fecal incontinence. Endosonography and histopathologic studies have demonstrated that age is related to sclerosis of the IAS (33, 34). Additionally, increased fiber density has been found in the EAS and pelvic floor muscles in study subjects older than 60 years of age (35). Degeneration of the sphincter causes a progressive decline in resting pressures and decreased sensation (36).

In the presence of a rectocele, the detached rectal mucosa prolapses during straining, which may cause excretion of mucous discharge from the mucosa for one to two hours following defecation (19). Incontinence of solid stool may also be seen. Procidentia is related to low rectal pressures and an obtuse anorectal angle, which can contribute to fecal incontinence. Most important, it appears that rectocele-induced straining at defecation causes a traction injury, which is most closely related to subsequent incontinence (14). It has been reported that patients with rectocele, but without evidence of neuropathy, remain continent (35). Additionally, after rectocele repair, patients with concomitant sphincter denervation remain incontinent (4).

Etiology

Despite similarities in the pathogenesis of fecal incontinence, the etiology of this disorder is highly variable (Table 4). As mentioned above, profuse diarrhea challenges normal continence secondary to an overwhelming increase in volume and impairment of rectal sensation. This may be associated with inflammatory bowel disease, radiation enteritis, laxative abuse, short gut syndromes, and acute diarrheal illness. However, it is most often seen with diabetes.

It has been estimated that 20% of diabetic patients experience fecal incontinence. Most have

TABLE 4
Conditions Associated with Fecal Incontinence

- Diarrheal states
  - inflammatory bowel disease (IBD)
  - irritable bowel syndrome (IBS)
  - infectious diarrhea
  - laxative abuse
  - malabsorption
- Anatomic defects
  - trauma
  - perineal/anorectal surgery
  - obstetric injury
- Neurologic impairment
  - diabetes
  - multiple sclerosis
  - cauda equina syndrome
  - stroke
  - neoplasms
- Overflow incontinence
  - fecal impaction
  - psychotropic drugs
  - antimotility agents
- Collagen vascular disease
  - systemic sclerosis
- Congenital abnormalities
  - myelomeningocele
  - spina bifida
- Pelvic floor denervation
  - idiopathic
  - descending perineum syndrome
- Aging

diarrhea and multiple neuropathies as well (37). The causes of diarrhea in diabetics with incontinence include autonomic dysfunction, bacterial overgrowth, ingestion of hexitols with osmotic diarrhea, and pancreatic insufficiency. Fecal incontinence may occur with the onset of diabetic diarrhea or it may follow years after the onset of diabetes has been documented. Nocturnal incontinence without warning is characteristic in these patients. Diarrhea in incontinent diabetics is rarely of high volume, but several studies indicate that one or more abnormalities of incontinence are present in the vast majority of these patients (38, 39). It is notable that unlike other causes of incontinence, fecal incontinence due to diabetes has a male predominance.

Patients with systemic sclerosis, or scleroderma, may experience gastrointestinal motility disturbances accompanied by symptoms of reflux, dysphagia, abdominal pain and defecatory difficulty. Incontinence receives less attention because it often goes unreported. Jaffin and colleagues (40) found that a tendency toward liquid and semi-formed stool and low resting pressure in the IAS in study subjects were likely contributors to incontinence in these patients. They also found that the RAIR was abnormal in 80% of subjects, but was normal in 70% of incontinent controls without systemic sclerosis. Because scleroderma affects smooth muscle more than striated muscles, EAS pressures in study subjects were normal or high when compared with incontinent controls without scleroderma.

Regrettably, many cases of fecal incontinence are iatrogenic in nature. Anal fistula repair requires sphincter division and is the most common operative cause of fecal incontinence (41). Additional procedural causes of incontinence include sphincterotomy, therapeutic anal dilation, and hemorroidectomy. The last has been associated with decreased intra-anal pressures (42, 43) and can also require removal of the anal cushions, with a subsequent decrease in rectal sensation (43). Prostatectomy has been associated with fecal incontinence in men. In one survey, Bishoff et al. (44) found the incidence of fecal incontinence to be 5% and 18% after radical perineal and retropubic prostatectomy, respectively. Fractures of the bony pelvis, which divide the PRM, may also be associated with incontinence.

Obstetric and birth trauma have long been recognized as significant factors in the etiology of fecal incontinence. Forceps, prolonged second stage (30), multiparity (30), and delivery of a large birth-weight infant (45) have all been associated with an increased risk of secondary incontinence.

There appear to be two major causes of incontinence related to childbirth: traumatic disruption of the sphincter muscles with neuropathy, resulting in early fecal incontinence, and isolated pudendal neuropathy, causing a late manifestation. Sultan et al. (46) reported that vaginal delivery is frequently associated with mechanical disruption of both the internal and external sphincters. This series found that 13% of primiparous and 23% of multiparous women who delivered vaginally had anal incontinence or fecal urgency when studied six weeks after delivery (46). Approximately 0.7% of vaginal deliveries with posterolateral episiotomies are associated with a third or fourth degree tear. These lacerations can cause sphincter and nerve injuries resulting in decreased resting and squeeze pressures. The internal anal sphincter appears to be injured more often and can be damaged even when the perineum remains intact. Episiotomies are usually repaired shortly after delivery, but inadequate primary repair with persistent incontinence may require secondary sphincter repair (3).

Stretching of the pudendal nerves during childbirth leads to progressive denervation of the anal sphincter muscles with resultant incontinence years later. Pudendal neuropathy causes a decrease in anal pressures, delayed conduction and decreased anal sensation (47). Idiopathic fecal incontinence in middle-aged women may be associated with prolonged pudendal latencies, which may be a late manifestation of childbirth injury.

It is noteworthy that the majority of patients with idiopathic fecal incontinence are women. Usually these are multiparous women with a history of vaginal delivery, high birth-weight infants, prolonged labor and/or forceps delivery. A history of a third or fourth degree perineal tear is not uncommon. As in incontinence related to obstetric injury, it is believed that pudendal nerve damage at delivery causes future dysfunction. In some reports, electromyograph (EMG) and histopathology studies have demonstrated denervation of the PRM and EAS muscles in up to 80% of patients with fecal incontinence (7).

Overflow incontinence is most commonly seen in elderly and institutionalized patients. Anatomical or functional outlet obstruction causes a leakage around the mass. The problem is often exacerbated by laxative abuse, which results in liquid stool seeping around the fecal bolus. Large neoplasms, such as lymphogranuloma, may also cause functional obstruction similar to that seen with constipation or encopresis in childhood.

Clearly, any neurologic deficit affecting the pelvic musculature can lead to incontinence. Neurogenic causes include multiple sclerosis, spinal cord injury, cauda equina syndrome of any etiology, and diabetes, as mentioned above. Lesions in the frontal cortex, usually associated with stroke, can also impair pelvic muscle function.

Descending perineum syndrome, a condition closely linked to fecal incontinence (48), may develop in patients with a long history of straining at defecation. This syndrome presents with chronic perineal aching and a vague sensation of a lump in the anal canal. When the patient strains to defecate, the perineum descends below the ischial tuberosity. This is probably secondary to stretch of the pudendal nerve during chronic straining.

As mentioned above, surgical insult or trauma can also lead to incontinence. It is important to recognize that causes of trauma include sexual abuse and anal intercourse. In working with patients with fecal incontinence, the physician must be prepared to approach these matters in a sensitive and nonjudgmental manner.

TABLE 5
Evaluation of Fecal Incontinence

- History
  - Stool patterns
    - frequency, duration
    - pattern of soiling
    - diurnal or nocturnal
    - urgency
    - diarrhea, constipation, straining
  - Associated symptoms or medical conditions
- Physical examination
  - Rectal examination
    - perineal inspection
    - anocutaneous reflex
    - digital exam to assess resting tone or squeeze pressure
    - PRM testing
  - Neurologic examination
    - mental status
    - sacral reflexes
    - perineal sensation

Diagnosis and Evaluation

Because fecal incontinence is a socially devastating condition, patients are often reluctant to discuss their experiences. Signs and symptoms need to be elicited directly. Patients should be asked to characterize their bowel movements, including the frequency, duration and pattern of incontinence. Inquiry should be made about daytime and nocturnal soiling and associated symptoms, such as urgency, lack of warning, diarrhea, constipation and straining.

History and physical examination should be focused to identify potential causes and conditions that may exacerbate fecal incontinence (Table 5). Pseudoincontinence, or perineal soiling caused by prolapsed hemorrhoids, perineal fistula, discharge from sexually transmitted disease and pruritus ani should also be excluded by history and physical examination. A complete history will note previous anorectal surgery or trauma, back injury, a history of functional bowel or inflammatory bowel disorders, diabetes, scleroderma, multiple sclerosis, stroke or other neurologic conditions. The physician should elicit a history of laxative abuse or other medication use. A dietary history to eliminate lactose, fructose, and sorbitol intolerance may be useful. An obstetric history, including number of vaginal deliveries, prolonged labor, forceps deliveries, episiotomies, and birth weights must be included, if applicable. A mental status examination and psychosocial testing may be useful, especially with the elderly and with children, where impaired motivation for continence may be a factor. Any history of sexual abuse or anal intercourse should be approached in a sensitive and nonjudgmental manner.

The physical examination should begin with inspection of the undergarments for soiling. It should also include careful inspection of the perianal area for any scars and obvious lacerations, fissures, or hemorrhoids. Prolapse or a gaping anus is often accompanied by urinary incontinence as well. Integrity of the sacral reflex arc can be assessed via the anocutaneous reflex, or "anal wink." This maneuver involves lightly scratching the perianal skin to elicit EAS contraction. The reflex may be absent in diabetics and in those with spinal cord injuries. Patients should also be assessed for gait and lower extremity sensory and motor function, to rule out cauda equina syndrome. The digital examination is useful in identifying a rectal mass or fecal impaction. One may also assess resting tone and strength of the PRM and EAS contraction by sensing the degree of contraction against the examining finger. The PRM is usually palpable posteriorly. The examination can be completed with anoscopy and flexible sigmoidoscopy. The rectum should be examined for the presence of ulceration or inflammation. Biopsy may be necessary to identify mucosal inflammation, neoplasm or ischemic changes. Evaluation of patients with diarrhea should include stool studies. These may include quantitative 24–72 hour stool samples for volume with measurement of stool electrolytes, osmolality, and fat to determine if high-volume diarrhea is osmotic or secretory in nature (Table 6). Culture and microscopic examination for ova and parasites also may be indicated.

TABLE 6
Diagnostic Studies for Fecal Incontinence

- Sigmoidoscopy
- Stool studies if diarrhea is present
- Anorectal manometry
    - test done with balloon catheters to test muscle function
    - resting pressures
    - squeeze pressures
    - sensation
    - compliance
    - sphincter response to distention
- Proctography and defecography
    - defines anatomy and change of pelvic floor muscle position with defecation
- Anorectal electromyography
    - examines muscle fibers to define muscular disorder
- Pudendal nerve conduction
    - tests how long it takes the "message" to get from nerve to muscle
- Endoanal ultrasound
    - assesses the integrity of the internal and external anal sphincters

Anal manometry is done with balloon catheters, to test the function of the sphincter muscles. Specifically, it can measure the resting tone of the IAS, squeeze pressures of the EAS and functional length of the high-pressure zone. In general, incontinent patients have lower squeeze and resting pressures than do controls (49, 50) (Fig. 2). Additional manometry studies can be used to assess the rectoanal inhibitory reflex, sensitivity, compliance and capacity (32). Manometry results correlate well with EMG studies used to assess the EAS.

EMG of the EAS can be performed with needles or surface electrodes. The sphincter can be examined in a circumferential pattern, by quadrant, or by the anterior/posterior positions. EMG can also be used to evaluate the PRM, by inserting a needle above the natal cleft. Denervation, conduction defects, and striated muscle function can all be evaluated with this study.

Pudendal nerve assessment (pudendal nerve terminal motor latency [PNTML]) tests how long it takes the "message" to get from the stimulated nerve to the muscle. Conduction of the pudendal nerve can be performed by using a St. Mark's electrode to stimulate the right and/or left pudendal nerves at the ischial tuberosities and then measuring the time to detect a muscle response. Such provocation of the pudendal nerve is most useful for assessment of neurogenic incontinence, obstetric injury and rectal prolapse. Patients with rectal prolapse and women with obstetric injury to the EAS may have prolonged PNTML (30).

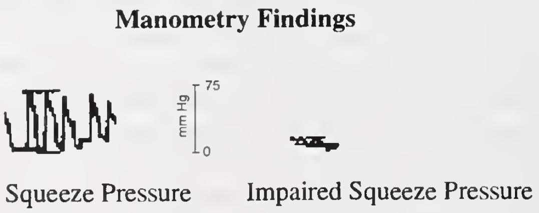

Fig. 2. Anal manometry. Pressure in millimeters of mercury. Normal is illustrated on the left.

Defecography, or the dynamic proctogram, defines the anatomy and change of the pelvic floor muscle position with defecation. It can identify abnormalities such as prolapse, perineal descent and intussusception. It can also assess PRM function. This procedure utilizes a paste of barium and potato powder to simulate fecal material. Video recording of strain, squeeze and defecation into a radiolucent commode allows real-time assessment of anatomic changes during defecation (51).

Endoanal ultrasound can identify structural defects of either the IAS or the EAS (52) (Fig. 3). This procedure is relatively noninvasive and is not time-consuming. Endosonographically, the sphincters appear distinctly as circular bands. Other pelvic floor structures, including the puborectalis muscle, the urethral sphincter, vagina and outlines of the bony pelvis and ischiorectal fossa, may be seen.

Treatment

The first step in the treatment of fecal incontinence is to address as many modifiable factors as possible. Dietary intolerance for sorbitol, lactose and fructose, should be considered, and substances should be eliminated as necessary, as well as increasing dietary fiber and adding bulking agents to solidify stool and enhance sphincter function. Conversely, patients with neurogenic

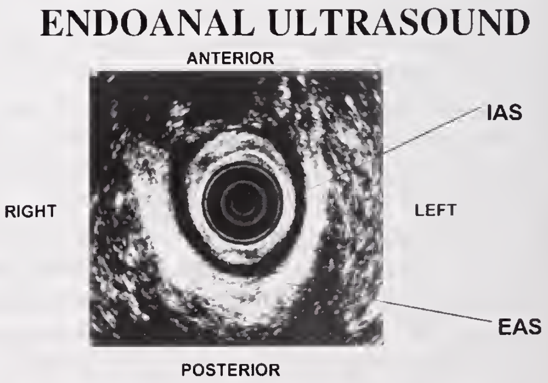

Fig. 3. Endoanal ultrasound. Note: Disruption of anterior external anal sphincter (EAS) and internal anal sphincter (IAS).

incontinence may benefit from a fiber-deficient diet, to decrease the volume of stool. Antacids containing magnesium should also be avoided, as they can cause diarrhea.

Opiate derivatives such as loperamide or diphenoxylate with atropine may decrease stool volume and frequency, improve stool consistency, or perhaps directly affect sphincter muscles. Some studies have shown that loperamide may be the more effective agent in improving anal pressures (53, 54) and may be the drug of choice when combined with a low-fiber diet to treat neurogenic incontinence.

In some cases, phosphate and warm tap-water enemas as needed can keep the rectum empty, and assist in regularly planned bowel movements. Constipation and overflow incontinence can be treated with hypertonic enemas, mineral oil enemas, and even manual disimpaction if necessary. In elderly or immobilized patients, enemas should be given once or twice daily until there are no more feces left in the colon or rectal vault. Follow-up should include enemas given at regular intervals, accompanied by a high fiber diet and generous fluid intake, to avoid recurrence. Psychotherapy may be indicated for those patients lacking motivation.

Biofeedback, an operant conditioning technique, has a response rate comparable to that of surgical treatments (55–57). It requires a motivated patient who can understand the process. In addition, the patient must have some rectal sensation and voluntary control of the EAS in order to generate a squeeze pressure. Biofeedback can be done by employing a manometer or anal EMG plug. Once the intra-anal sensor is in place, the response is recorded for the patient. A patient can look at tracings of muscle strength and work toward enhancing his or her response. The rectal balloon is inflated with volumes of air and the patient learns to recognize this as rectal distention (sensory discrimination). The smallest volume of distention sensed by the patient is determined and the threshold is then lowered progressively until the response becomes automatic and no further improvement occurs.

Patients also can be taught to increase EAS sphincter pressure, in response to rectal distention via visual feedback from manometric recordings, by practicing contracting the EAS. This technique can be used when rectal distention or urgency is sensed. Most adult patients respond after just one session.

The large number of surgical procedures employed for fecal incontinence suggests that no single technique is best in all cases. Sphincter repair is usually reserved for isolated defects and for cases where medical therapy has failed. Surgery is often considered as first-line therapy in rectal prolapse, as resuspension restores continence in two-thirds of the patients (58). Obstetrical injuries, trauma and acute disruption of the sphincter are usually managed by primary repair of the defect. Results are usually better with solid rather than liquid stool (14).

There are a number of surgical techniques available to address fecal incontinence that has been unresponsive to medical therapy. Direct apposition requires mobilization of the EAS, resection of scar tissue, muscle division, and an end-to-end repair. The procedure has a 33.5–77.5% success rate (59). Postanal repair has been useful for neurogenic and idiopathic incontinence. The levator ani, PRM and EAS are plicated posteriorly to restore the anorectal angle and tighten the anal canal. Anterior plication is the preferred approach, with a satisfactory outcome in 62% of patients with idiopathic incontinence and 71% with a traumatic etiology (60). Generally, surgery is less likely to be successful if neuropathy is present prior to repair.

Overlapping anterior sphincteroplasty can be employed to treat childbirth injuries. This procedure involves identification of healthy tissue on either side of the defect, division of scar tissue and overlapping repair of the sphincter. Normal PNTML is predictive of a good outcome with sphincterotomy (61).

Anal encirclement uses a silver wire or, more recently, a Silastic ring or rod to mechanically tighten the anus, creating a barrier to the passage of feces. These procedures are often unsatisfactory, with frequent complications including impaction, infection and erosion of the encircling material. Implantable artificial sphincters are also available.

Skeletal muscle transpositions using the gluteus maximus, gracilis or palmaris longus muscles have been performed for fecal incontinence. In graciloplasty, first described in 1952, the gracilis muscle is mobilized to preserve the proximal attachments and maintain the neurovascular supply. An implantable nerve stimulator may be utilized to achieve sustained contraction (62).

Colostomy is reserved for failures of medical, biofeedback, and surgical techniques. Colostomy has been advocated for immobile patients who suffer from severe skin breakdown and complications including sepsis related to fecal incontinence.

Conclusion

Fecal incontinence is a devastating, but potentially treatable, condition. It is a significant problem affecting up to 20% of hospitalized patients and more than 2% of the general community. This condition primarily affects women, and is often associated with sphincter disruption and/or nerve injury after vaginal delivery. It is also associated in older patients with such common conditions as diabetes and stroke. It is important to understand the pathophysiology of incontinence and to recognize specific abnormalities, using objective tests of anorectal function described here. Evaluation begins with sensitive history-taking and a physical examination; even the most conservative treatments may have a significant impact on a patient's quality of life.

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GERD and Its Complications

Stuart Jon Spechler, M.D.

Abstract

Gastroesophageal reflux disease (GERD) is the condition that results when gastric material that refluxes into the esophagus or oropharynx causes symptoms, tissue injury, or both. Endoscopic examination usually is not required merely to establish a diagnosis of GERD, but endoscopy is the best diagnostic test for Barrett's esophagus, a sequela of GERD that predisposes to esophageal adenocarcinoma. Patients found to have Barrett's esophagus will require regular endoscopic surveillance for early, curable neoplasia. Esophageal pH monitoring is useful for patients who have symptoms or signs suggestive of GERD, but who have little or no response to antisecretory therapy. For patients who have severe, ulcerative reflux esophagitis, the clinician has only two reasonable therapeutic options: (1) lifelong antisecretory therapy with proton pump inhibitors or (2) antireflux surgery. There are no absolute indications for antireflux surgery, but the operation can be considered for patients with severe GERD who are unwilling to accept lifelong medical therapy or for young patients whose GERD symptoms respond only to proton pump inhibitors administered in high dosages. **Key Words:** Gastroesophageal reflux disease.

Gastroesophageal reflux disease (GERD) is the condition that results when gastric material that refluxes into the esophagus or oropharynx causes symptoms, tissue injury, or both (1). Reflux-induced esophageal injury (reflux esophagitis) can be complicated by the development of esophageal erosions and ulcerations. Esophageal ulcerations that stimulate the deposition of fibrous tissue result in esophageal strictures, and ulcerated esophageal squamous epithelium can be replaced by a metaplastic, intestinal-type epithelium that has a malignant predisposition (a condition called Barrett's esophagus). Refluxed gastric juice that crosses the upper esophageal sphincter to enter the oropharynx can damage the oropharyngeal mucosa and erode the dental enamel. Aspiration of refluxed material into the airway can result in laryngitis and pulmonary disorders such as asthma and bronchitis. Thus, GERD can have both esophageal and extra-esophageal manifestations. The esophageal symptoms of GERD such as heartburn and odynophagia usually respond quickly and dramatically to conventional medical antireflux therapy (2). In contrast, resolution of the extra-esophageal symptoms of GERD may require high doses of potent acid-suppressive medications administered for many months (3).

Who Needs Endoscopy?

For patients with GERD, an endoscopic examination of the esophagus can answer the four clinical questions listed below:

- Is there reflux esophagitis?
- Is the esophagitis severe?
- Is there an esophageal stricture?
- Is there Barrett's esophagus?

Answers to these questions may have clinical importance in certain situations. For example, the endoscopic demonstration of reflux esophagitis establishes a diagnosis of GERD, and the demonstration of severe esophagitis suggests that med-

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ical treatment with agents other than proton pump inhibitors will not be effective. The demonstration of an esophageal stricture indicates that esophageal dilation may be required in addition to intensive antisecretory therapy. Furthermore, endoscopy is required to establish a diagnosis of Barrett's esophagus.

The clinician should appreciate that endoscopy does not always answer the question, "Does the patient have GERD?" Although the endoscopic finding of reflux esophagitis establishes a diagnosis of GERD, a normal endoscopic examination does not eliminate GERD as a cause of symptoms. Gastroesophageal reflux can cause disabling symptoms without causing visible esophageal damage (4). Endoscopic examination reveals esophagitis in fewer than 50% of patients who complain of frequent heartburn (1), and the esophagus typically appears normal endoscopically in patients who only have extra-esophageal symptoms of GERD (5). Patients with classic heartburn who respond readily to conventional antireflux therapy can be assumed to have GERD, and endoscopy is not necessary simply to confirm that diagnosis. Without endoscopic examination, however, it is not possible to answer all of the four clinical questions listed above. For patients with GERD symptoms, the physician must decide whether the benefits of answering these questions outweigh the inconvenience, small risk, and considerable expense of endoscopy. The American Society for Gastrointestinal Endoscopy (6) has recommended diagnostic endoscopy for patients who have "esophageal reflux symptoms which are persistent or recurrent despite appropriate therapy," and has advised that diagnostic esophagogastroduodenoscopy (EGD) is generally not indicated for evaluating "uncomplicated heartburn responding to medical therapy" (6). More recently, the Practice Parameters Committee of the American College of Gastroenterology (7) has endorsed a similar policy. This policy states: "If the patient's history is typical for uncomplicated GERD, an initial trial of empiric therapy (including lifestyle modification) is appropriate. Patients in whom empiric therapy is unsuccessful or who have symptoms suggesting complicated disease should have further diagnostic testing." Presumably, symptoms that might suggest complicated disease would include fever, anorexia, weight loss, dysphagia, odynophagia, and bleeding. The policy further states that "selected individuals who have longstanding symptoms or who require continuous therapy may need endoscopic screening for Barrett's esophagus." Although these proposed approaches to patient management seem reasonable, it is important to recognize that they are merely committee recommendations whose efficacy has not been established by formal clinical investigation. Also, there is no clear consensus regarding which is the most appropriate medication to use for initial empiric therapy of GERD, i.e., a histamine H2-receptor blocker, a prokinetic drug, or a proton pump inhibitor. Proton pump inhibitors clearly are most effective for eliminating the signs and symptoms of GERD, but the H2-blockers and prokinetics will control symptoms in most patients who have GERD of mild to moderate severity. Patients with GERD whose symptoms are refractory to H2-blocker therapy tend to have severe and complicated disease. For such patients, early diagnostic evaluation may be important to tailor therapy and to prevent further complications. Therefore, I usually begin empiric therapy for GERD with an H2-blocker, and reserve the use of proton pump inhibitors (PPIs) for patients whose diagnosis has been established by endoscopic examination.

Who Needs 24-Hour Esophageal pH Monitoring?

Ambulatory monitoring of esophageal pH can be used to document the pattern, frequency, and duration of acid reflux, and to seek a correlation between reflux episodes and symptoms (8, 9). In most ambulatory systems, an episode of acid reflux is defined (somewhat arbitrarily) as a drop in esophageal pH below 4. Standard 24-hour pH monitoring records a number of different variables such as the total number of reflux episodes, the number of episodes longer than 5 minutes in duration, and the duration of the longest episode. The single most clinically applicable variable appears to be the total percentage of the monitoring period that esophageal pH remains below 4 (9). In normal individuals, esophageal pH remains below 4 for less than 4.5% of the 24-hour monitoring period. Most patients who have both endoscopic signs and symptoms of GERD also have abnormal 24-hour esophageal pH monitoring studies, whereas subjects with no such signs and symptoms usually have normal studies. It is difficult to determine the precise sensitivity and specificity of the test, however, because there is no universally accepted "gold standard" for the diagnosis of GERD.

In theory, protracted esophageal pH monitoring should be very useful in establishing acid reflux as the cause of symptoms in individual patients. In practice, however, the correlation between discrete episodes of acid reflux and symptoms often is poor. For example, although normal individuals often experience brief episodes of acid reflux during the day (particularly after meals), these episodes usually are not associated with heartburn (10). Even in patients with heartburn who have endoscopic evidence of reflux esophagitis, 24-hour esophageal monitoring reveals that fewer than 20% of episodes of acid reflux are accompanied by heartburn (11).

For patients who have classic symptoms of GERD, endoscopic evidence of reflux esophagitis and a good response to conventional antireflux therapy, ambulatory esophageal pH monitoring usually is a superfluous test that provides little important clinical information. For patients with atypical symptoms, the test occasionally can be useful to establish an association of symptoms with abnormal acid reflux. Perhaps the best application of 24-hour esophageal pH monitoring is for patients who have symptoms or signs suggestive of GERD, but who have little or no response to potent antisecretory therapy. For such patients, the test is often most useful if antisecretory therapy is continued during the monitoring period. The objective demonstration that antisecretory therapy has successfully eliminated acid reflux, but that symptoms persist nevertheless, indicates that acid reflux is not the cause of the symptoms. Alternatively, the demonstration that acid reflux persists despite antisecretory therapy suggests that alternative antireflux therapies must be used. For patients with extra-esophageal symptoms such as hoarseness, esophageal pH monitoring during therapy should not be performed until the patient has had treatment for an adequate period of at least 2–3 months.

Who Needs Proton Pump Inhibitors?

The proton pump inhibitors (e.g., omeprazole, lansoprazole, rabeprazole, pantoprazole) are the most effective medications available for the treatment of GERD. In patients with mild to moderately severe reflux esophagitis treated with conventional doses of these agents, healing rates of 80–100% can be expected within 8 weeks (7, 12–14). The efficacy of any medication for GERD is inversely proportional to the severity of the underlying esophagitis, and patients with severe, ulcerative reflux esophagitis often do not respond well to H2-blocker therapy (15). PPIs have been shown to heal esophagitis that is refractory to H2-blocker treatment, and therefore PPIs appear to be the agents of choice for the medical treatment of patients who have severe forms of reflux esophagitis. Very severe (grade 4) reflux esophagitis may persist despite PPI therapy administered in conventional dosages in up to 40% of cases. In almost all such cases, however, the severe reflux esophagitis that is refractory to conventional dose PPI therapy can be healed simply by increasing the dose of the PPI (16). Also, recent studies have shown that PPI treatment can improve dysphagia and decrease the need for esophageal dilation in patients who have peptic esophageal strictures (17, 18). Therefore, PPI therapy also is indicated for the medical treatment of patients with peptic strictures.

Although PPIs are highly effective in healing esophagitis, they do little to correct the underlying diathesis for reflux. In the majority of patients with severe GERD, symptoms recur shortly after stopping these agents and maintenance therapy usually is required. For most patients, the dose of PPI necessary to maintain remission is at least the dose required to heal the acute esophagitis (19). Furthermore, for patients with severe GERD, the maintenance dose of PPI may increase with time. Klinkenberg-Knol et al. recently studied a group of patients with severe GERD, all of whom had been refractory to H2-blockers (16). The patients were treated with a high dose of omeprazole, and the esophagitis healed in every case. Patients then were switched to maintenance omeprazole in a dose of 20 mg per day, and were followed for up to 5 years. During that time, almost one-half of the patients had a relapse of GERD despite maintenance therapy. In every case, the esophagitis could be healed again simply by increasing the dose of omeprazole. By years 3–5, a substantial number of patients required double and triple doses of omeprazole to maintain remission. Also, 11% of the patients developed substantial elevations of their serum gastrin levels. This study shows that PPIs can heal esophagitis very effectively over the long term if one is willing to pay the price, both in dollars and in the potential for side effects.

Recent studies suggest that a course of PPI therapy can be used as a diagnostic test for GERD-related symptoms. In one study of 37 patients with atypical chest pain who had heart disease excluded by a cardiologic evaluation, endoscopy and 24-hour pH monitoring were performed at baseline to establish an objective diagnosis of GERD (20). In a double-blind, placebo-controlled, crossover trial, patients were randomly assigned to receive either omeprazole (40 mg AM, 20 mg PM) or placebo for one week. Omeprazole treatment resulted in a > 50% decrease in chest pain (a positive omeprazole test) in 78% of patients with GERD, whereas only 14% of patients without GERD had such a response. The authors estimated that the omeprazole test for GERD-associated noncardiac chest pain had a sensitivity of 78% and a specificity of 86%, and resulted in a cost-saving of $573 per patient compared to a conventional diagnostic work-up that might include an endoscopy and/or 24-hour pH monitoring study.

Who Needs Laparoscopic Antireflux Surgery?

Different antireflux operations such as the Nissen fundoplication, the Hill posterior gastropexy, and the Belsey fundoplication all share several fundamental features (21). In all of these procedures, the surgeon creates an intra-abdominal segment of esophagus, reduces the hiatal hernia, approximates the diaphragmatic crura, and wraps a portion of the gastric fundus around the distal esophagus. As a result, the surgery narrows the angle of His (the angle formed by the junction of esophagus with stomach) which may create an antireflux flap-valve effect (22). Restoration of the distal esophagus to the positive pressure environment of the abdomen also may prevent reflux. Reduction of the hiatal hernia and approximation of the diaphragmatic crura may restore the normal antireflux function of the crural diaphragm. The fundoplication itself may act as a one-way valve, and may prevent distention of the gastric fundus that can trigger transient lower esophageal sphincter (LES) relaxations. Finally, LES pressures increase after fundoplication for reasons that are not clear.

A large cooperative study conducted in the late 1980s compared the efficacy of available medical and surgical therapies for GERD (23). The 247 study subjects all had GERD complicated by Barrett's esophagus, esophageal ulceration, esophageal stricture, or severe erosive esophagitis. Antireflux lifestyle modifications were prescribed for all study subjects regardless of treatment group. Patients were randomly assigned to receive one of three types of treatment: continuous medical therapy, symptomatic medical therapy, or surgical therapy. Continuous medical therapy included antacid tablets and ranitidine taken on a daily basis regardless of symptoms; metoclopramide and sucralfate were added in a stepwise fashion for patients who remained symptomatic. For patients in the symptomatic medical therapy group, drug therapy was used only for control of symptoms. Therapy in these patients began with antacid tablets; ranitidine, metoclopramide, and sucralfate were added in a stepwise fashion for symptoms that could not be controlled with antacids alone. Patients in the surgical therapy group had Nissen fundoplications. All three therapies resulted in significant improvements in the symptoms and endoscopic signs of GERD for up to two years. However, surgical therapy was significantly better than either medical therapy for the two-year duration of the study. Overall satisfaction with therapy also was better for patients in the surgical group. Although this prospective, randomized study predated the availability of omeprazole, the investigation clearly demonstrated that surgical therapy is superior to medical therapy without proton pump inhibitors. Although there is no reported study that has compared the efficacy of antireflux surgery with proton pump inhibitors, it is anticipated that the results of these two forms of therapy will be similar.

Antireflux surgery now can be performed laparoscopically, and a number of reports have described the short-term results of laparoscopic fundoplication (24–26). For the Nissen fundoplication, these results can be summarized in Table 1.

These complication rates, mortality rates, and outcome results are comparable to those reported for the open procedure (27). Compared to the open procedure, the expected advantages of laparoscopic fundoplication are listed in Table 2.

Presently, there are few published data that substantiate all of the proposed advantages for laparoscopic fundoplication over the open procedure (28). Fundoplication performed by a skilled surgeon is a highly effective form of therapy for GERD whether the operation is done by the open or laparoscopic approach. At least one study has shown that the primary factor involved in postoperative patient satisfaction is the relief of GERD

TABLE 1
Results of Laparoscopic Nissen Fundoplication

Complication rate	4–26%
Mortality rate	< 1%
Conversion to open procedure	2–14%
Median hospital stay	2–7 days
Good or excellent outcome	> 85%

TABLE 2
Proposed Advantages for Laparoscopic Antireflux Surgery (Compared to Open Procedure)

Fewer complications	Faster return to work
Less postoperative discomfort	Better esthetic result
Shorter hospital stays	Greater patient satisfaction
Less expensive	

symptoms rather than the operative approach (open vs. laparoscopic) (29). These findings suggest that the availability of laparoscopic surgery should not influence the physician's decision regarding the advisability of fundoplication. The primary decision for the clinician is whether or not the patient should have an antireflux operation, not how the operation should be performed.

Major indications for antireflux surgery include the following:

- Patients with severe GERD who are unwilling to accept lifelong medical therapy.
- Patients who have signs and symptoms of GERD (esophageal or extra-esophageal) that are responsive only to PPIs administered in high dosages.
- Patients who are young and require longtime use of PPIs for GERD control.

Although none of the above can be considered absolute indications for antireflux surgery, the option should at least be considered and discussed with the patient. Lifelong medical therapy for severe GERD is expensive, and there are theoretical risks involved. The patient should be well informed of the risks and benefits of both medical and surgical treatments for GERD.

Note that medical intractability is not listed as an indication for antireflux surgery. Prior to the advent of PPIs, internists primarily recommended antireflux surgery for patients whose GERD failed to respond to medical therapy. Today, this practice is not tenable. Modern medical therapy is extraordinarily effective in healing reflux esophagitis, and it is decidedly unusual to encounter patients who are truly refractory to medical treatment. Indeed, the very diagnosis of GERD must be questioned for patients whose esophageal signs and symptoms are unaffected by the administration of PPIs in high dosages. It is ironic that in an era when highly effective medical therapy for GERD is available, surgical therapy is best reserved for patients who are medical successes, not failures. Patients who respond well to medical therapy usually do well with fundoplication surgery. In the large majority of patients whose symptoms fail to respond to PPIs, esophageal pH monitoring reveals that these agents have controlled acid reflux. Such patients almost certainly would have a poor response to antireflux surgery.

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Grand Rounds

Regulation of Urea Transporter Proteins in Kidney and Liver

Jeff M. Sands, M.D.

Abstract

Due to urea's role in producing concentrated urine, its transport is critically important to the conservation of body water. Within the renal inner medulla, urea is transported by both facilitated and active urea transport mechanisms. The vasopressin-regulated, facilitated urea transporter (UT-A1) in the terminal inner medullary collecting duct (IMCD) permits high rates of transepithelial urea transport and results in delivery of large quantities of urea into the deepest portions of the inner medulla where it is needed to maintain a high interstitial osmolality for maximal urine concentration. Four cDNA isoforms of the UT-A urea transporter family have been cloned. In addition, there are three secondary active, sodium-dependent, urea transport mechanisms in IMCD subsegments: (1) active urea secretion in the apical membrane of the terminal IMCD from untreated rats; (2) active urea absorption in the apical membrane of the initial IMCD from low-protein fed or hypercalcemic rats; and (3) active urea absorption in the basolateral membrane of the initial IMCD from furosemide-treated rats.

This review will focus on integrative studies of the rapid and long-term regulation of urea transporters in rats with reduced urine concentrating ability. These studies led to the surprising result that the basal-facilitated urea permeability in the terminal IMCD and UT-A1 protein abundance are increased during in vivo conditions associated with an impaired urine concentrating ability. In contrast, there are two response patterns of active urea transporters: (1) hypercalcemia, a low-protein diet, and furosemide result in induction of active urea absorption in the initial IMCD, albeit by different mechanisms, and inhibition of active urea secretion in the terminal IMCD; while (2) water diuresis results in up-regulation of active urea secretion in the terminal IMCD without any active urea absorption in the initial IMCD. The first pattern contributes to the urine concentrating defect by increasing urea delivery to the base of the inner medulla, thus decreasing urea delivery distally to the inner medullary tip. The second response pattern will directly decrease urea content in the deep inner medulla.

UT-A urea transporters are also expressed outside the kidney. Recent studies show that the liver has phloretin-inhibitable urea transport and that it occurs via a 49 kDa UT-A protein. When rats are made uremic, the abundance of this 49 kDa UT-A protein increases in the liver *in vivo*. This up-regulation of the 49 kDa UT-A protein may allow hepatocytes to increase ureagenesis to reduce the accumulation of ammonium and/or bicarbonate in uremia. **Key Words:** Urea, urea transporter, vasopressin, urine concentrating mechanism, collecting duct.

Introduction

Urea plays a unique and important role in the urinary concentrating mechanism. Its importance to generating a concentrated urine has been appreciated since 1934 when Gamble and colleagues (1) described "an economy of water in renal function referable to urea." Maximal urine concentrating ability is decreased in protein-deprived or malnourished humans or animals, and is restored by urea infusion (1 – 8). Thus, any solution to the question of how the inner medulla concentrates urine needs to take into account some effect derived from urea. The passive mechanism for urinary concentration (9, 10) requires that the inner medullary interstitial urea concentration exceed the urea concentration in the lumen of the thin ascending limb. If an inadequate amount of urea is delivered to the deep inner medulla, then the chemical gradients necessary for passive NaCl absorption are not established and urine concentrating ability is reduced. The major mechanism for delivering urea to the inner medullary interstitium is urea absorption across the terminal inner medullary collecting duct (IMCD) (11). We reported evidence for facilitated (or carrier-mediated) urea transport across the terminal IMCD in 1987 (12). Subsequently, four cDNA isoforms of the urea

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transporter (UT-A) family have been cloned (Table) (13 – 19), and polyclonal antibodies against urea transporter proteins are now available (14, 20, 21).

UT-A Urea Transporter Proteins

UT-A1 protein is expressed in the apical membrane of the rat terminal IMCD; urea transport is stimulated by vasopressin when UT-A1 is heterologously expressed in *Xenopus* oocytes (13, 18, 20, 22). UT-A2 is expressed in thin, descending limbs of short-looped nephrons (20). Urea transport is not stimulated by cAMP analogs when UT-A2 is heterologously expressed in either *Xenopus* oocytes or human embryonic kidney cells (13, 15, 16, 18, 19, 22, 23). UT-A1 and UT-A2 share identical 3' cDNA and C-terminal amino acid sequences, but differ at their 5' (N-terminal) ends (13). Thus, UT-A2 is basically the C-terminal half of UT-A1 (Fig. 1). UT-A3 has the same 5' cDNA and N-terminal amino acid sequence as UT-A1 but has a unique 3' (C-terminal) end and is basically the N-terminal half of UT-A1 (19). Although UT-A4 has the same 5' and 3' cDNA, and ` and C-terminal amino acid sequences as UT-A1, it is smaller than UT-A1 and basically consists of the N-terminal quarter of UT-A1 spliced into the C-terminal quarter of UT-A1 (19). Both UT-A3 and UT-A4 mRNAs are expressed in kidney medulla (although their exact tubular location is unknown), and neither is expressed in cortex (19). Both UT-A3 and UT-A4 are stimulated by cAMP analogs when heterologously expressed in human embryonic kidney cells, suggesting that both are regulated by vasopressin (19).

Antibodies have been made to the C-terminus (20, 21) and intracellular loop region (14) of UT-A1. Based upon the cDNA sequence of the four UT-A isoforms, the C-terminus antibody should detect UT-A1, UT-A2, and UT-A4, while the loop region antibody should detect only UT-A1 (14, 19, 24). Western blots of inner medullary tip proteins generally show bands at 97 and 117 kDa using either antibody (14, 20, 21). Preliminary studies suggest that both the 97 and 117 kDa proteins are glycosylated versions of UT-A1 (25). UT-A1 protein is most abundant in the inner medullary tip, present in the inner medullary base, and not present in outer medulla or cortex (20, 26), consistent with the pattern of facilitated urea permeabilities measured in perfused rat collecting duct segments (11, 12, 27, 28).

Functional studies show that phloretin-inhibitable urea transport is present in both the apical and basolateral membranes of the rat terminal IMCD, with the apical membrane being the rate-limiting barrier for vasopressin-stimulated urea transport (29). UT-A1 immunostaining is observed in the apical membrane and intracellular cytoplasmic vesicles of the rat terminal IMCD, but no immunostaining is seen in the basolateral membrane (20). Recently, Wade and colleagues (30) identified a 67 kDa UT-A protein in the basolateral membrane of the rat terminal IMCD, suggesting that it may be the basolateral membrane urea transporter.

Rapid Regulation of UT-A1

Vasopressin. Adding vasopressin to the bath of a perfused rat terminal IMCD results in vasopressin binding to V_2-receptors, stimulating adenylyl cyclase, generating cAMP, stimulating protein kinase A (PKA), and ultimately increasing facilitated urea permeability (12, 31 – 34). One possible mechanism for this increase is regulated trafficking of UT-A1, as suggested by comparison

TABLE

UT-A Facilitated Urea Transporter Family

Isoform	Synonym	mRNA (kb)	MW (kDa)	AVP Stim	Location	References
UT-A1	UT1	4	97; 117	Yes	IMCD	(13, 14, 18, 20)
UT-A2	UT2	2.9	55	No	tDL	(15 – 17, 20)
UT-A3		2.1	4	Yes	Medulla*	(19)
UT-A4		2.5	60	Yes	Medulla*	(19)

Isoform names are based upon the systematic nomenclature for urea transporters proposed in reference 60.
mRNA size is based upon northern analysis.
Molecular mass (MW) is based upon western analysis.
AVP Stim = stimulation by arginine vasopressin. AVP Stim is based upon an increase in urea flux by vasopressin in heterologous expression systems (*Xenopus* oocytes, human embryonic kidney cells).
IMCD = inner medullary collecting duct.
tDL = thin descending limb.
Medulla* — exact tubular location unknown.

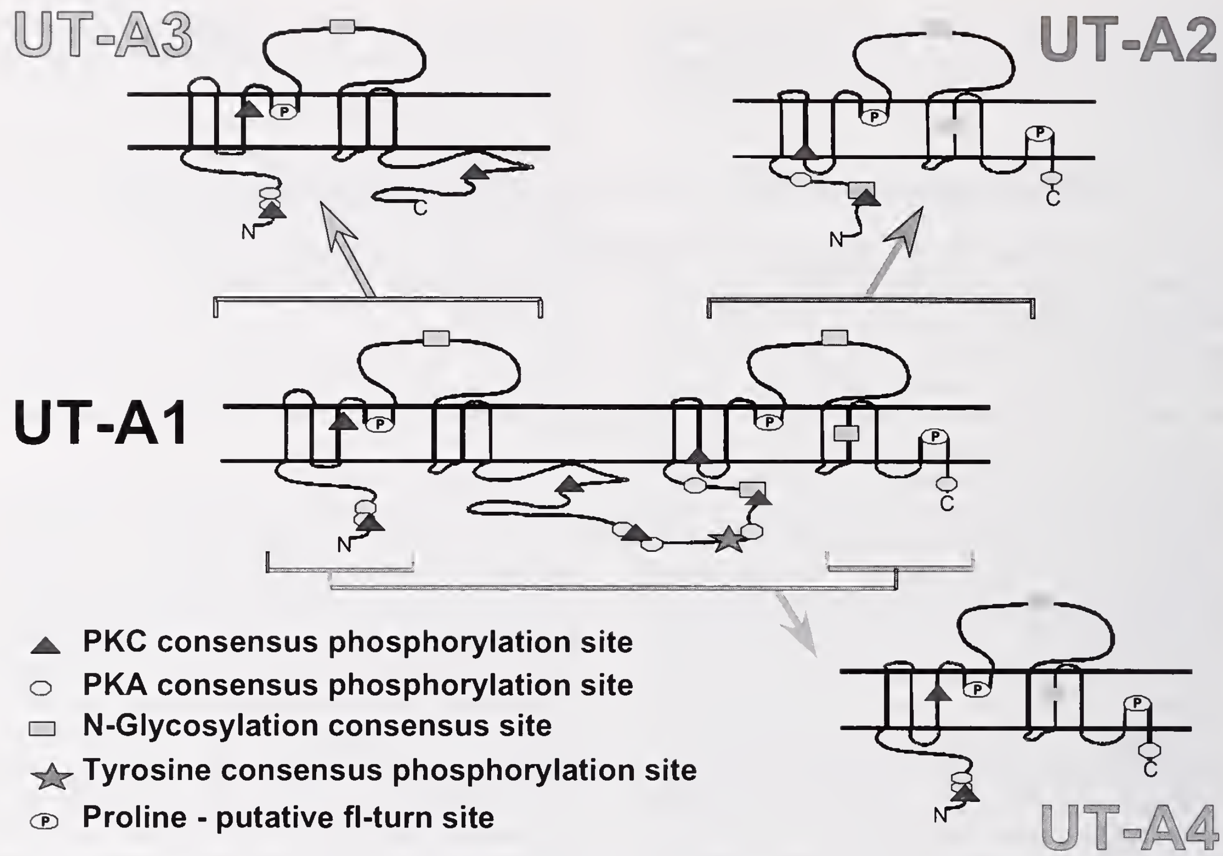
UT-A3
UT-A2
UT-A1
UT-A4
P
N
C
▲ PKC consensus phosphorylation site
○ PKA consensus phosphorylation site
▭ N-Glycosylation consensus site
★ Tyrosine consensus phosphorylation site
Ⓟ Proline - putative fl-turn site

Fig. 1. Diagram illustrating a model of the predicted membrane topology for the four UT-A proteins and illustrating the structural relationships between them. Consensus sequences for phosphorylation or glycosylation are indicated. This figure is modified from reference 19.

to the mechanism by which vasopressin regulates aquaporin-2 (AQP2), the vasopressin-regulated water channel (AQP2 and UT-A1 have similar immunolocalization patterns and both are regulated rapidly by vasopressin [12, 20, 35]). However, Knepper and colleagues tested for regulated trafficking of UT-A1 in the rat terminal IMCD and showed that, in contrast to AQP2, trafficking of UT-A1 between the apical membrane and sub-apical vesicles does not occur (36). An alternative mechanism is that vasopressin alters the phosphorylation of UT-A1. The deduced amino acid sequence for UT-A1 contains several consensus sites for phosphorylation by PKA, as well as protein kinase C (PKC) or tyrosine kinase (19). However, no studies testing this potential regulatory mechanism have been published.

Hyperosmolality. Increasing osmolality, either by adding NaCl or mannitol to both the perfusate and bath of a perfused rat terminal IMCD, increases facilitated urea permeability, independently of vasopressin (34, 37, 38). When osmolality is increased in the presence of vasopressin, there is an additive stimulatory effect on facilitated urea permeability (32, 34, 37, 38). Both hyperosmolality- and vasopressin-stimulated facilitated urea permeability are inhibited by phloretin or thiourea (31, 37). However, increases in intracellular calcium (39) mediate hyperosmolality-stimulated facilitated urea permeability while increases in adenylyl cyclase mediate vasopressin-stimulated facilitated urea permeability (33). Thus, both hyperosmolality and vasopressin rapidly increase facilitated urea permeability, but they do so via different second messenger pathways.

Long-Term Regulation of UT-A1

Vasopressin. Two methods have been used to study whether vasopressin exerts a prolonged regulatory effect on IMCD-facilitated urea permeability and UT-A1 protein abundance: water loading or restriction to vary endogenous vasopressin levels; or administering exogenous vasopressin or dDAVP (desmopressin, a V_2-selective vasopressin agonist) to Brattleboro rats (which have congenital central diabetes insipidus due to the lack of endogenous vasopressin). Increasing plasma vasopressin by either method decreases the abundance of both the 97 and 117 kDa UT-A1 proteins in rat inner medulla (14). Consistent with this change in UT-A1 protein abundance, a perfused terminal IMCD from water loaded (3 days) rats has a higher basal and vasopressin-stimulated facilitated urea permeability than a terminal IMCD from rats given water *ad libitum* (40). Thus, these studies led to the surprising result that facilitated urea permeability and UT-A1 protein abundance are decreased when vasopressin levels are increased (i.e., down-regulation of UT-A1).

In response to either water loading or restriction, northern analysis shows no change in UT-A1 mRNA abundance (16, 18, 22), suggesting that the changes in facilitated urea permeability and UT-A1 protein abundance are not regulated by transcription. In contrast, UT-A2 mRNA abundance does fall in the inner medulla of water loaded (3 days) rats and rises in: (1) water-restricted (3 days) rats; (2) rats receiving dDAVP for 3 weeks; and (3) Brattleboro rats treated with vasopressin for 1 week (16, 18, 41). Recently, Wade and colleagues showed that administering dDAVP for 7 days to Brattleboro rats increases UT-A2 protein abundance in thin, descending limbs (42). Thus, regulation of UT-A2, but not UT-A1, could involve transcriptional mechanisms stimulated by vasopressin (43). No studies of the long-term regulation of UT-A3 or UT-A4 have been published.

Impaired urine concentrating ability. To address the question of whether UT-A1 is regulated both rapidly and long term by vasopressin, similar to the way that AQP2 is regulated by vasopressin, we tested the long-term regulation of UT-A1 in four animal models associated with a reduction in urine concentrating ability: water diuresis; low-protein diet; hypercalcemia; and furosemide diuresis (44). We predicted that a decrease in urine concentrating ability could result from: (1) a decrease in urea absorption and down-regulation of UT-A1 in the inner medullary tip; or (2) an increase in urea absorption and up-regulation of UT-A1 in the inner medullary base.

We found that in all four conditions, basal (no vasopressin) facilitated urea permeability was increased in the deepest portion of the IMCD (located in the inner medullary tip), the $IMCD_3$, and there was greater abundance of the 117 and 97 kDa UT-A1 proteins in the inner medullary tip (14, 21, 23, 40, 45–49). Surprisingly, therefore, basal facilitated urea permeability and UT-A1 protein abundance are increased during *in vivo* conditions associated with an impaired urine concentrating ability and a reduced plasma vasopressin level. This suggests that rather than the UT-A1 urea transporter being up-regulated to generate urine concentrating ability, it may be up-regulated to prevent further reductions in urine concentrating ability and/or to reduce the loss of urea from the inner medulla during conditions with high urine flow rates. This could be a mechanism explaining the rapid increase in urine concentrating ability that occurs within 5–10 minutes after urea is infused into people, rats, or dogs who were malnourished or fed low-protein diets (1, 2, 4, 50): UT-A1 protein abundance is increased when urine concentrating ability is impaired and this response "prepares" the IMCD to restore inner medullary urea rapidly once urea (or protein) intake rises.

Role of glucocorticoids. Facilitated urea permeability was measured in perfused initial and terminal IMCD subsegments from rats undergoing adrenalectomy, adrenalectomy plus replacement with a physiologic dose of glucocorticoid (dexamethasone), or sham-operation. Compared to sham-operated rats, basal-facilitated urea permeability in the rat terminal IMCD was significantly increased in adrenalectomized rats and reduced in dexamethasone-treated rats (21). In contrast, there was no difference in basal- or vasopressin-stimulated facilitated urea permeability in the initial IMCD between the three groups of rats (21). Next, western analysis was performed on membrane or vesicle fraction proteins from the inner medullary tip or base, corresponding to the location of the terminal or initial IMCD, respectively. UT-A1 protein abundance was significantly increased in both membrane and vesicle fractions from the inner medullary tip of adrenalectomized rats (21). In contrast, there was no change in UT-A1 protein abundance in the inner medullary base (21). Northern analysis showed no change in UT-A1 mRNA abundance in either inner medullary region (21). Thus, glucocorticoids down-regulate the function and expression of UT-A1 in the rat terminal IMCD.

Diabetic rats. Next, we studied rats with uncontrolled diabetes mellitus, since this condition is associated with enhanced urea excretion and an increase in urinary corticosterone. Thus, diabetic rats provide a second *in vivo* model for testing the role of glucocorticoids in down-regulating UT-A1. Rats were made acutely diabetic by injecting streptozotocin (125 mg/kg body weight). UT-A1 protein abundance was significantly decreased in the inner medullary tip, but unchanged in the inner medullary base, of diabetic rats (47). AQP2 protein abundance was unchanged in the inner medulla, indicating that the decrease in UT-A1 was not a generalized, nonspecific response (47).

To determine whether the decrease in UT-A1 protein abundance was mediated by glucocorticoids, rats underwent adrenalectomy, adrenalectomy plus streptozotocin, and adrenalectomy plus streptozotocin plus replacement with a physiologic dose of glucocorticoid (51). Adrenalectomy blocked the decrease in UT-A1 protein due to diabetes, and glucocorticoid-replacement restored the diabetes-induced decrease (47). Thus, glucocorticoids are mediators of the reduction in UT-A1 protein in the inner medullary tip of rats with diabetes mellitus (47). This effect is independent of insulin, since insulin was missing from all three groups of rats (47).

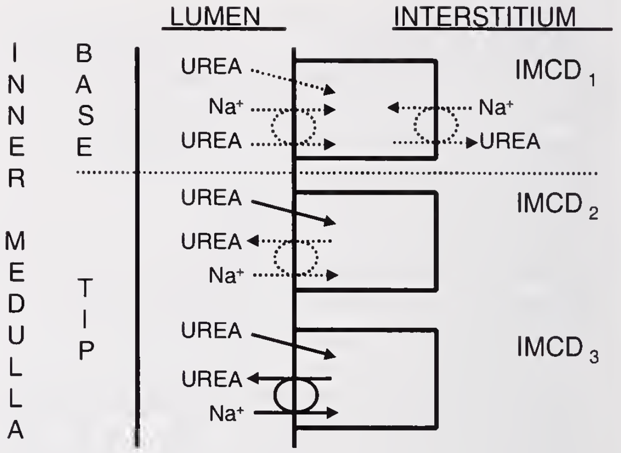

Fig. 2. Urea transporters expressed in rat inner medullary collecting duct subsegments. Collecting duct cells are illustrated starting at the inner-outer medullary border (IMCD$_1$, top) through the papillary tip (IMCD$_3$, bottom) (61, 62). The tubule lumen is shown on the left side of each cell. Arrows represent facilitated urea transporters. Circles connecting two arrows represent active urea transporters. Solid symbols represent urea transporters expressed in untreated rats. Dashed symbols represent urea transporters expressed only in rats with reduced urine concentrating ability. Top cell: an IMCD$_1$ cell showing a facilitated urea transporter that is induced in low-protein fed or hypercalcemic rats (45, 46, 49), and two inducible, Na^+-dependent, active urea transport processes, one of which is a Na^+-urea "co-transporter" in the apical membrane of low-protein fed (53) or hypercalcemic (48) rats, and the other, a Na^+-urea "counter-transporter" in the basolateral membrane of furosemide diuretic rats (54). Middle cell: an IMCD$_2$ cell showing a facilitated urea transporter (UT-A1) that is expressed in the apical membrane of untreated rats (12, 20) and is up-regulated by hypercalcemia, furosemide, or adrenalectomy (21, 40, 49), and a Na^+-dependent, active urea "counter-transporter" that can be induced in the apical membrane of water diuretic rats (48). Bottom cell: an IMCD$_3$ cell showing a facilitated urea transporter (UT-A1) that is expressed in the apical membrane of untreated rats (12, 20) and is up-regulated in low-protein, hypercalcemia, furosemide, or adrenalectomy (21, 40, 48, 49), and a Na^+-dependent, active urea "counter-transporter" that is expressed in the apical membrane of untreated rats (12, 20, 52). This Na^+-urea "counter-transporter" is up-regulated in water diuretic rats (52) and down-regulated in a low-protein fed, (48), hypercalcemic (48), or furosemide diuretic (54) rats.

Active Urea Transport

In rats given food and water *ad libitum*, we found no active urea transport in the IMCD$_1$ (initial IMCD) or IMCD$_2$ (52) (Fig. 2). However, we did find active urea secretion in the IMCD$_3$ (52). This active urea secretion is: (1) inhibited by removing sodium (and replacing it with N-methyl-D-glucamine) from the tubule lumen (but not from the bath), suggesting an apical membrane localization; (2) stimulated rapidly by vasopressin; and (3) inhibited by phloretin or ouabain (52). These functional properties suggest that this is a secretory "sodium-urea counter-transporter" in the apical membrane of the IMCD$_3$ (52).

Next, we tested for active urea transport in IMCD subsegments from the four rat models associated with an impaired urine concentrating ability: low-protein diet; hypercalcemia; water diuresis; and furosemide diuresis. We found similar responses in rats fed an 8% protein diet for 3 weeks and in rats made hypercalcemic by feeding them a vitamin D analog, dihydrotachysterol, for 3 days. Active urea absorption was induced in the IMCD$_1$ from both low-protein fed and hypercalcemic rats. It was completely inhibited by: (1) removing sodium from the perfusate (and replacing it with N-methyl-D-glucamine) but not from the bath, suggesting an apical membrane localization; and (2) adding ouabain to the bath (45, 48, 53). These functional properties suggest that this is a reabsorptive "sodium-urea co-transporter" in the apical membrane of the IMCD$_1$. There was no active urea transport in the IMCD$_2$ from low-protein fed or hypercalcemic rats, and active urea secretion was completely inhibited in the IMCD$_3$ from low-protein fed or hypercalcemic rats (45, 48).

We also found active urea absorption in the IMCD$_1$ from furosemide-treated rats (54). In contrast to the active urea absorption in the IMCD$_1$ induced by low-protein feeding or hypercalcemia (45, 48, 53), this one is: (1) inhibited by removing sodium (and replacing it with N-methyl-D-glucamine) from the bath (but not from the perfusate), suggesting a basolateral membrane localization; (2) stimulated rapidly by vasopressin; and (3) inhibited by phloretin or ouabain (54). These functional properties suggest that this is a reabsorptive "sodium-urea counter-transporter" in the basolateral membrane of the IMCD$_1$. This active urea transport process is functionally similar to the sodium-urea counter-transporter in the IMCD$_3$ from rats given food and water *ad libitum*, but transports urea in an opposite direction and is localized to the opposite cell membrane. At present, it is not possible to determine whether there are two sodium-urea counter-transporters, or a single transporter that can be sorted to different cell membranes depending upon the IMCD subsegment and the *in vivo* condition of the rat. There was no active urea transport in the $IMCD_2$ from furosemide-treated rats, and active urea secretion was completely inhibited in the $IMCD_3$ (54).

In contrast to the preceding three animal models, we found no active urea transport in the $IMCD_1$ from water diuretic rats (52). However, we found that water diuresis results in a significant increase in active urea secretion in the $IMCD_3$ and its induction in the $IMCD_2$, the middle portion of the IMCD, (48, 52). Thus, in contrast to the uniform pattern of long-term regulation of facilitated urea permeability, there are two response patterns of active urea transporters when urine concentrating ability is reduced: (1) hypercalcemia, a low-protein diet, and furosemide result in induction of active urea absorption in the $IMCD_1$, albeit by different mechanisms, and inhibition of active urea secretion in the $IMCD_3$; while (2) water diuresis results in up-regulation of active urea secretion in the $IMCD_3$ and its induction in the $IMCD_2$, without any active urea absorption in the $IMCD_1$ (45, 46, 48, 52–54).

These patterns of change in active urea transporters are consistent with our predictions about changes in urea transport and urine concentrating ability (*vide supra*). In the first response pattern (hypercalcemia, a low-protein diet, and furosemide), the induction of active urea absorption in the $IMCD_1$ contributes to the urine concentrating defect by increasing urea delivery to the base of the inner medulla, thereby decreasing urea delivery distally to the inner medullary tip; the accompanying inhibition of active urea secretion in the $IMCD_3$ may prevent an even greater reduction in urea content in the deep inner medulla. In the second response pattern (water diuresis), up-regulation of active urea secretion in the terminal IMCD subsegments (the $IMCD_2$ and the $IMCD_3$) will directly decrease urea content in the deep inner medulla.

Urea Transport in Liver

The only mammalian tissue which has phloretin-inhibitable urea transport, other than kidney and erythrocytes, is the liver (55–57). This suggests that liver cells may express a urea transporter protein in order to accelerate urea efflux following ureagenesis (55, 58). We tested whether a cultured human liver cell line, HepG2 cells, transports urea by measuring thiourea influx. HepG2 cells had a high thiourea influx rate that was significantly inhibited by two urea transport inhibitors, phloretin and thionicotinamide (59). Western analysis of HepG2 cell lysate using our antibody to the C-terminus of UT-A1, which detects UT-A1, UT-A2, and UT-A4, revealed two protein bands, 49 and 36 kDa (59). We found the same proteins in cultured rat hepatocytes, freshly isolated rat hepatocytes, and in liver from rat, mouse, and chimpanzee (59). Deglycosylation of rat liver lysate had no effect on either band, and both bands were present when analyzed by native gel electrophoresis (59). Differential centrifugation of rat liver lysate showed that the 49 kDa UT-A protein is in the 200,000xg (membrane) fraction while the 36 kDa UT-A protein is in the cytoplasmic fraction (59).

Next, we made rats uremic by 5/6th nephrectomy and feeding them a high protein diet to determine whether the abundance of these UT-A proteins varies *in vivo*. The 49 kDa UT-A membrane protein was significantly increased in livers from uremic rats compared to pair-fed, control rats (59). Thus in liver, phloretin-inhibitable urea transport occurs via a 49 kDa UT-A protein, and uremia increases the abundance of this UT-A protein *in vivo*. This up-regulation of the 49 kDa UT-A protein may allow hepatocytes to increase ureagenesis to reduce the accumulation of ammonium and/or bicarbonate during uremia.

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Grand Rounds

Hepatitis C Virus, Autoimmunity and Lymphoproliferation

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Abstract

We summarize clinical, laboratory and pathologic details regarding a patient who presented with extrahepatic disease manifestations of hepatitis C virus (HCV) infection, including cryoglobulinemic leg ulcers due to cutaneous vasculitis, peripheral sensorimotor neuropathy, and recurrent pulmonary infiltrates. The patient had evidence for B-cell lymphoproliferation, diagnosed as extranodal lymphoma on initial (though not subsequent) bone marrow examination, retroperitoneal lymphadenopathy, and the presence of a Type II IgMκ monoclonal rheumatoid factor which became cryoprecipitable on complexing to IgG. Chronic hepatitis was mild on liver biopsy, though fibrotic changes developed over a three-year period of follow-up. She had consistently normal liver function tests, except for a brief rebound effect on discontinuing interferon-alpha, and preterminally. Symptoms were only partially responsive to trials of corticosteroids, cytotoxic agents, plasmapheresis and interferon, and the patient ultimately died at The Mount Sinai Hospital of sepsis. We review current information regarding the spectrum of extrahepatic HCV infection, including pathogenic factors relevant to its overlapping autoimmune, rheumatic and lymphoproliferative disease manifestations. The exact prevalence of these HCV-related syndromes among the 1% of the world population estimated to be infected by this virus remains to be delineated. Chronicity of infection, and lack of efficacy of currently available therapy in effecting sustained clearance of the virus from the host, have made this an important public health problem that is likely to increase in significance. Possible relationships to non-Hodgkin's lymphoma may present novel opportunities to delineate the basis for oncogenesis in HCV infection. **Key Words:** Cryoglobulinemia, hepatitis C virus, non-Hodgkin's lymphoma, autoimmunity, vasculitis.

Introduction

Hepatitis C virus (HCV) is an RNA virus that is a member of the *Flaviviridae*, a family which includes members that are both hepato- and lymphotropic, and may be associated with chronic infectious diseases. The genome of this virus was first reported ten years ago using reverse cloning techniques on the blood of a chimpanzee infected by what was then termed "non-A, non-B" hepatitis (1). In the time since that report, much descriptive information has accumulated regarding the persistence of HCV, potential mechanisms utilized by the virus to escape host immune responses, and limited response to therapies such as interferon-alpha. The availability of accurate serologic tests and assays to directly or indirectly quantitate viral RNA in biological fluids has led in turn to a virtual disappearance of HCV from the nation's blood supply, heretofore a major mode of transmission, and a significant downturn in the number of new infections reported each year. It has also led to an awareness of large reservoirs of chronically infected individuals, many of whom are apparently asymptomatic, or who have disease manifestations that do not clearly imply chronic liver disease (2).

It is estimated that 3.9 million persons in the United States are HCV antibody (HCVAb) positive (i.e., 1.8% of the population; 0.1–0.7% of healthy blood donors), of whom 2.7 million are HCV RNA positive, and therefore considered to be chronically infected (3); this percent increases dramatically if specific populations of patients (e.g., hemophiliacs, intravenous drug abusers, HIV-infected individuals) are surveyed. Of the

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dialysis population, 10–40% are HCVAb positive. This population of patients poses particular diagnostic and therapeutic challenges, because HCV may be a cause of chronic renal disease, and may manifest differently in this setting; also, specific therapeutic issues arise relating to chronic renal insufficiency and potential problems with immunomodulatory therapies in the post-renal transplant patient (4, 5). Although HCV accounts for about 20% of community-acquired acute viral hepatitis, 40–50% of patients give no clear-cut history of infection. Fifty to 80% of infected individuals become chronically infected (versus 2–5% persons infected with hepatitis B virus). About 50% of infected persons have normal or minimally elevated liver function tests (LFTs) (2, 3). Furthermore, elevations in liver function tests may be intermittent, reflecting to some extent spontaneous variations in viral RNA that may change over a range as high as log 6 (10^6) variations in viral copy number in serum with time, allowing the possibility that infection may be missed unless multiple samplings are made (6, 7). Of those chronically infected, 20–35% progress to cirrhosis, and a significant number will go on to develop hepatocellular carcinoma; consequently, HCV is now the major cause of these two conditions in the United States. The average time to cirrhosis is 10 years, to hepatocellular carcinoma 29 years. Each year, eight to ten thousand persons die of liver-associated complications of HCV, and one thousand undergo liver transplantation; of those transplanted, approximately 40% will develop a recurrence of hepatitis in the allograft and many will require specific therapy and/or another transplant (8, 9).

More accurate and sensitive testing techniques have also made it clear that extrahepatic disease manifestations may provide subtle complications of chronic infection, or in turn dominate its course. These extrahepatic manifestations of HCV infection include both autoimmune phenomena and frank autoimmune and/or rheumatic diseases, as well as an association with B-cell lymphoproliferation and possibly non-Hodgkin's lymphoma. The following is illustrative of these various aspects of HCV infection.

Case History

A 70-year-old woman was transferred to The Mount Sinai Hospital for management of pulmonary infiltrates.

Ten years previously, she had first developed recurrent episodes of purpura, occurring mostly below knees and around the ankles, increased by standing, not related to ambient temperature, which would resolve spontaneously after about a week. Over the year before her initial evaluation, she noted the purpuric lesions to also be associated with numbness and decreased sensation, mostly involving the dorsal foot and lower third of both legs.

Five years previously, she came to the vascular and dermatology clinics for evaluation and treatment of large leg ulcers that had developed around and above both lateral malleoli (Fig. 1A). Biopsy of a purpuric lesion showed leukocytoclastic vasculitis; she was started on corticosteroids, and referred to Rheumatology for further evaluation. Initial work-up at that time included normal blood count and liver function tests (LFTs), urinalysis significant for red blood cells and proteinuria, and a type II monoclonal mixed cryoglobulin present at a concentration of 1.36 mg/mL in serum. Serum values for IgG — 480 mg/dL (normal range, 800–1700); IgM — 247 mg/dL (60–370); IgA — 133 mg/dL (85–450); rheumatoid factor (RF) — 594 IU (<20); antinuclear antibody (ANA) negative; C3 — 105 mg/dL (75–135); C4 — 8 mg/dL (10–40). Analysis of 24-hour urine samples revealed 1013–1300 mg protein; creatinine clearance (Ccr) was 82 mL/minute (normal, 85–175 mL/min); monoclonal IgMk in serum and cryoglobulin, with urine negative for monoclonal proteins by immunoelectrophoresis. HCVAb were positive by recombinant immunoblot assay (RIBA), but hepatitis A and B serologies were negative. HCV RNA was detected in both serum and cryoprecipitate, genotype 1b.

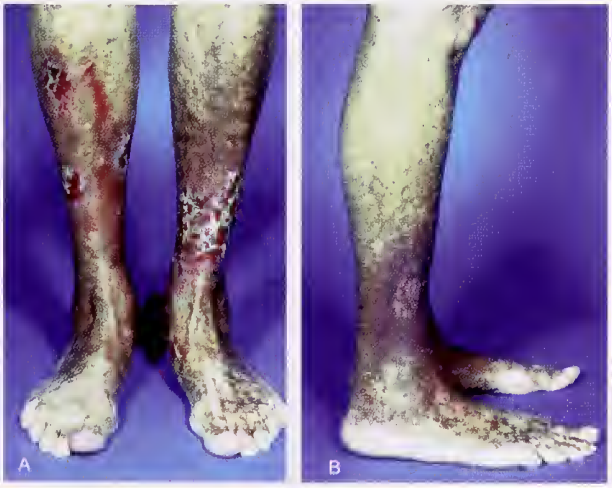

Fig. 1. Anterior view of patient's legs, showing multiple leg ulcers and palpable purpura at the time of initial evaluation (**A**). A lateral view several months later (**B**), following local and systemic therapy, shows complete healing and subsidence of purpuric lesions.

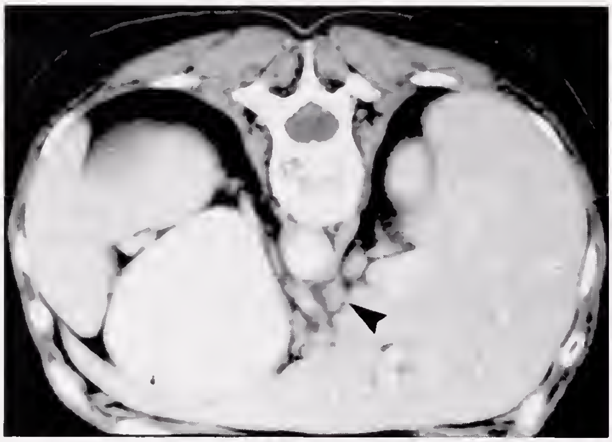

Fig. 2. CT of the abdomen, showing a 1.2 cm lymph node (arrowhead) adjacent to the aorta. Also noted on this study were smaller pretracheal, precarinal and periportal nodes (not shown).

Proteinuria and hematuria were initially attributed to a 6.5 x 5.0 cm cyst involving the upper pole of the left kidney, which was seen on ultrasound, with renal scan showing 39% function in the left kidney, and 61% in the right. A bone marrow aspiration and biopsy showed multiple nodules of small lymphoid cells, consistent with lymphoma, small lymphocytic type; as shown in Fig. 6A. The CT scan of the abdomen showed significant retroperitoneal lymphadenopathy, an example of which is shown in Fig. 2. Electrophysiologic testing confirmed a sensorimotor axonal polyneuropathy.

The patient was treated for hypertension, and received care for her leg ulcers; prednisone was continued. A trial of plasmapheresis was poorly tolerated, and she was started on chlorambucil, with subsequent resolution of ulcers (Fig. 1B) and diminution of purpura and cryoglobulin levels. Treatment had been suspended four years previously because of the development of estrogen receptor-positive breast carcinoma, requiring a radical left mastectomy, subsequent chemotherapy, and tamoxifen maintenance therapy.

Purpura, cryoglobulinemia (2.1 mg/mL) and leg ulcers had recurred three years previously, at which time IgG levels were found to range from 240–423 mg/dL; IgA — 146–153 mg/dL; IgM — 211–249 mg/dL; C4 — 9 mg/dL; relative serum viscosity — 1.6 (normal range, 1.4–1.8); C3 — 93 mg/dL; LFTs normal; RF — 1208 IU/dL; and 24-hour protein — 1517 mg. CT of the abdomen again showed periportal (1.2 cm), pericaval (1.2 cm) and aortocaval (<1 cm) adenopathy (Fig. 2), along with mild hepatomegaly and a normal-sized spleen. Liver biopsy revealed chronic hepatitis, minimal activity, with no fibrosis; the biopsy was positive for HCV RNA by reverse transcription (RT) *in situ* polymerase chain reaction (PCR) amplification; genotype Ib. Electrophysiologic studies were unchanged from the previous study.

Two years previously, following the liver biopsy, she had been started on interferon-alpha (IFNα), 3M units three times per week, which she

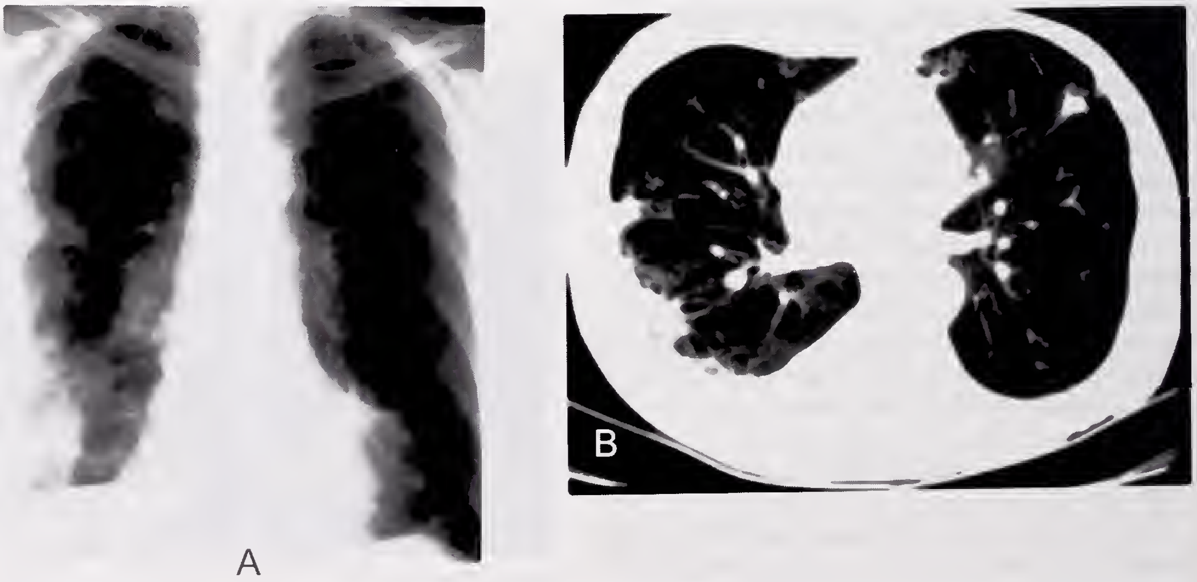

Fig. 3. **A**. Chest X-ray taken to evaluate cough and dyspnea, which developed five months after the initiation of therapy with IFNα, shows new right upper and lower lobe peripheral infiltrates, and a right-sided pleural effusion. **B.** A CT scan of the chest taken shortly thereafter shows bilateral subpleural nodular infiltrates, all of which resolved spontaneously over the following two months.

tolerated for five months before it was discontinued because of the development of cough, dyspnea and a chest X-ray showing a new right upper lobe infiltrate, and pleural and parenchymal changes at the right base (Fig. 3A and B). During this period, there was no significant diminution in HCV RNA viral load, assessed by quantitative PCR (Amplicor^{TM}, Roche Molecular Systems, Somerville, New Jersey), or of the cryoglobulin level (Fig. 4A), though a significant redistribution of HCV RNA from the cryoprecipitate to the serum supernatant was noted over this time period (Fig. 4B). Increased LFTs, proteinuria (3805 mg), and cryoglobulinemia (2.4–2.83 mg/mL) were noted over the 2–3 months following discontinuance of the drug (Fig. 4B), along with gradual resolution of the pulmonary lesions on serial CT studies of the chest.

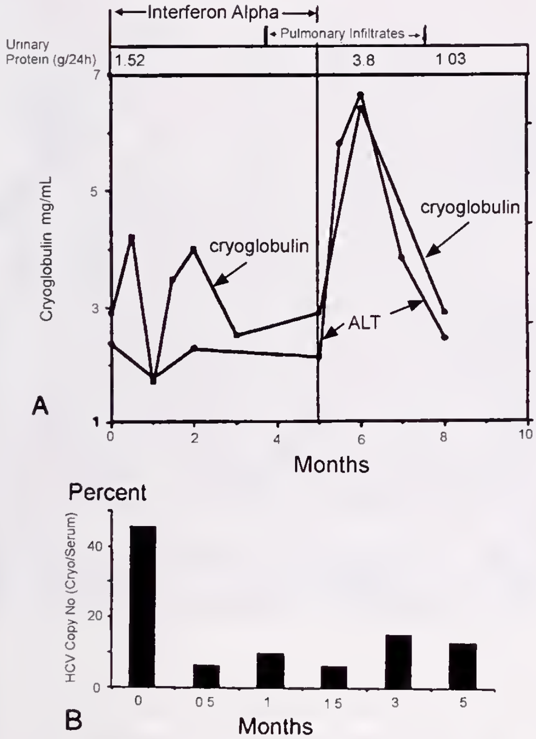

Fig. 4. Cryoglobulin quantitation and serum alanine aminotransferase (ALT) levels during and following discontinuance of therapy with IFN (**A**). Treatment with interferon-alpha was given during the first 5 months, as shown. Although no clinical or apparent biochemical response was seen, there was a striking redistribution of HCV RNA from the cryoprecipitate to the serum supernatant (**B**), possibly due to altered stoichiometry of cryoprecipitable and noncryoprecipitable HCV-containing immune-complexes. In retrospect, pulmonary infiltrates may have been a manifestation of the disease (86), and the striking increase in proteinuria, ALT levels (which had never been abnormal previously), cryoglobulins, and total HCV copy number (not shown) following discontinuance of IFNα may have been a "rebound" phenomenon (80). Normal levels for ALT are 0–40 IU/L.

Leg ulcers required increasingly aggressive wound care over the three months before her final admission, during which time period an elevation of γ-glutamyl transpeptidase (GGTP) — 172 IU/L (normal range, 8–69) and increasing IgM (to 525 mg/dL) were noted; HCV RNA — 690, 885 copies/mL; 24-hour protein — 6600 mg; Ccr — 23 mL/min. Two months previously, she was admitted to another hospital for fever to 102°C, chills, cough, anasarca and dyspnea, with new right perihilar and left upper lobe infiltrates and bilateral pleural effusions on chest X-ray and CT of the chest. She was treated initially with ciprofloxacin for a presumed community-acquired pneumonia; however, all cultures were negative. She then received high doses of intravenous corticosteroids, without any favorable response, but with increasing azotemia and hyperglycemia. On transfer to The Mount Sinai Hospital, leg ulcers and active lower extremity purpura were again noted; BUN — 81 mg/dL (normal range, 8–26); AST — 131 IU/L (5–40); ALT — 138 IU/L (0–40); alkaline phosphatase — 419 IU/L (35–125); GGTP — 2409 IU/L; albumin — 2.6 g/dL; IgM — 700 mg/dL; cryoglobulins — 1.29 mg/mL. A follow-up bone marrow aspiration and biopsy, were negative; however, a monoclonal B-cell population was identified by flow cytometry. Abdominal ultrasound and MRI were both consistent with cirrhosis with ascites. Laparoscopic liver and kidney biopsies confirmed active hepatitis, now with septal fibrosis, and hepatic glomerulosclerosis. Steroids were gradually tapered, and plasmapheresis initiated to reduce the level of cryoglobulins. Hospital course was complicated by treatment for purulent drainage of leg ulcers culturing methicillin-resistant *Staph. aureus* and *Pseudomonas*. Preterminally, she became acutely short of breath and was found to have new right upper lobe consolidation on chest X-ray. She died of septic shock, with blood cultures positive for *Pseudomonas*, in spite of broad-spectrum antibiotic coverage, and hemodynamic and ventilator support.

Autopsy

The right upper lobe infiltrate was a severe bronchopneumonia (Fig. 5A) which had disseminated to eventuate in septic shock; no viral inclusions or hyphae were found. In addition to the lobar pneumonia (Fig. 5B), diffuse adenopathy and foci of chronic inflammation, consisting mostly of mature lymphocytes (Fig. 5B), were also noted. Careful review of bone marrow at several sites failed to confirm lymphomatous

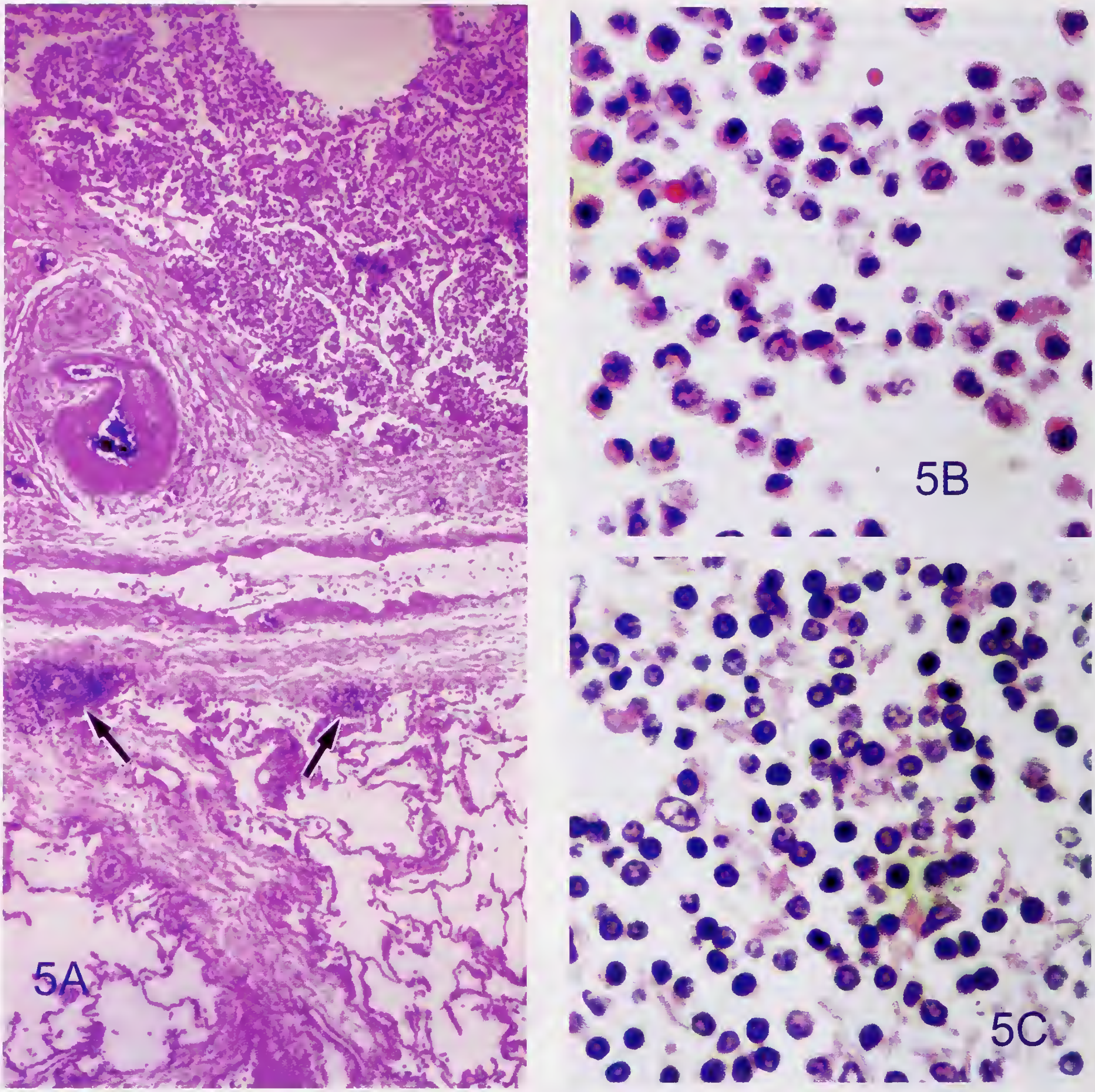

Fig. 5. Sections of the right lung taken at autopsy: (**A**) At low power, portions of the upper lobe (top) and middle lobe (bottom) are separated by the sparsely cellular interlobar septum (horizontal band extending across the middle of the figure). The upper lobe alveoli contain a dense infiltrate of acute inflammatory cells and debris (H&E, 20x). Normally, expanded alveoli in the middle lobe are filled with air. (**B**) At higher magnification, the intra-alveolar inflammatory cells are almost exclusively neutrophils, with multilobated nuclei and ample cytoplasm; (H&E, 400x). By contrast, foci of chronic inflammation seen within the interlobar septum (see arrows in **A**) are composed of lymphocytes, with a single round nucleus and a narrow rim of cytoplasm (H&E, 400x). (**C**) In contrast, foci of chronic inflammation in the interlobar septum (arrows in 5A) consist of lymphocytes with a single round nucleus and a narrow row of cytoplasm (H&E, 400x).

involvement that had been seen previously (Fig. 6A). The spleen was congested without evidence of malignant transformation; however (consistent with the previous CT findings), several lymph nodes were enlarged, with effacement of normal architecture by mature-appearing lymphocytes, collections of which were also noted at several other sites (Figs. 6 B–D). The left kidney had a 6 x 4 x 4 cm retention cyst in its upper lobe; renal vasculature was diffusely involved by moderate arterial and arteriolar intimal thickening with hyaline deposition and focal fibrinoid necrosis. Glomeruli showed mild mesangial widening with pale reticulated matrix and lobulation, consistent with hepatic glomerulosclerosis. The liver weighed 2,300 grams and showed diffuse conges-

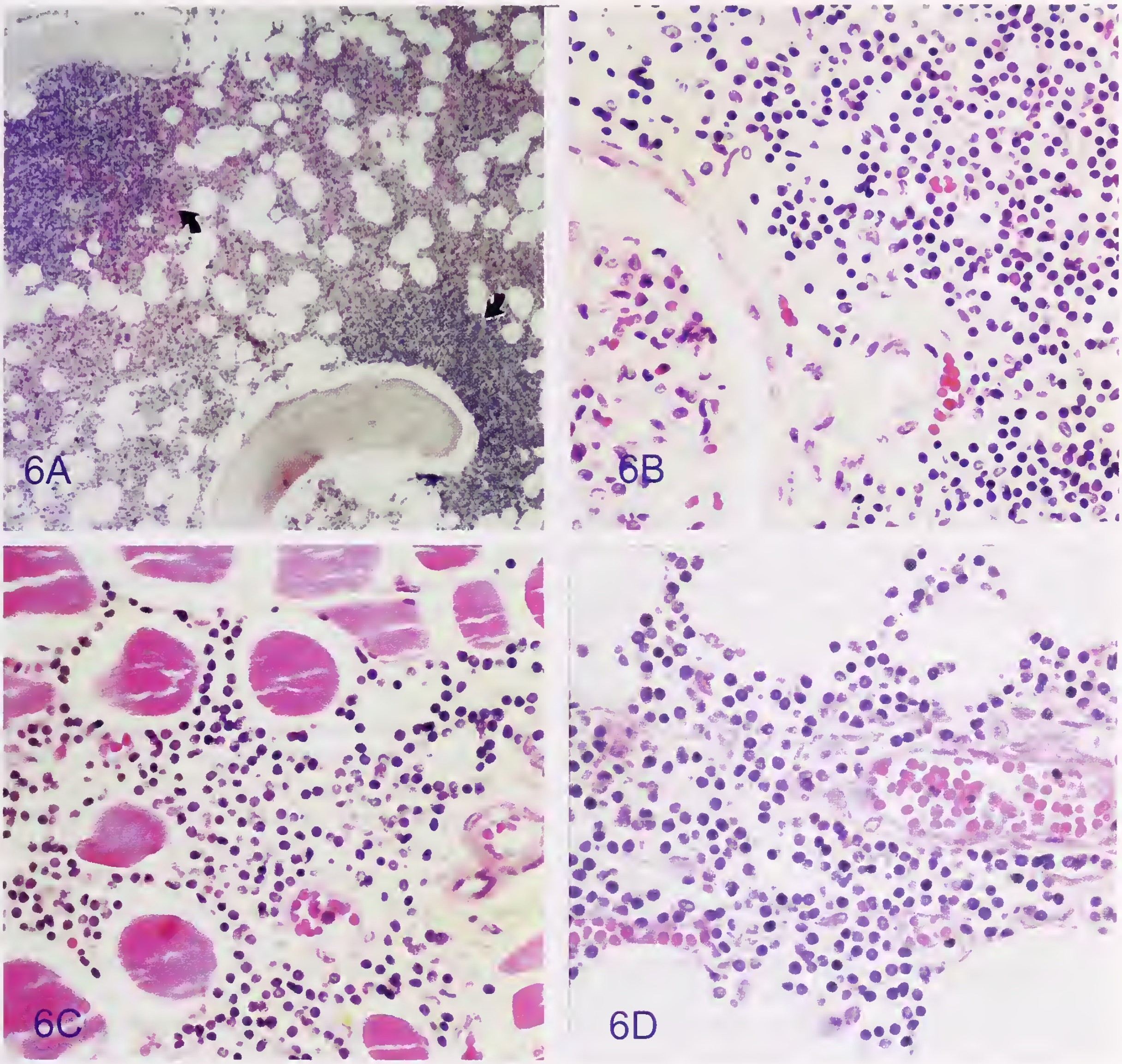

Fig. 6. (**A**) A bone marrow biopsy done at the time of initial evaluation in 1993 revealed dense aggregates of darkly staining cells (arrows) adjacent to the bony trabeculae (H&E, 40x). Higher magnification revealed small mature lymphocytes, consistent with a diagnosis of chronic lymphocytic leukemia/small lymphocytic lymphoma. Sections taken at autopsy reveal dense infiltrates of lymphocytes in a variety of tissues, including kidney (**B**), skeletal muscle (**C**), and mesenteric soft tissue (**D**) (all H&E, 200x).

tion and steatosis; on cut surface, there was interstitial fibrosis, but not nodular cirrhosis; microscopically, portal spaces were found to be involved with dense collections of mature-appearing lymphocytes (Fig. 7A), in addition to incomplete bridging portal fibrosis and bile ductular proliferation (Fig. 7B).

TABLE 1

Mixed Cryoglobulinemia

- Cutaneous vasculitis-purpura/leg ulcers
- Arthralgia/arthritis
- Immune complex nephritis
- Neuropathy
- Inflammatory liver disease
- IgM rheumatoid factor
- Hypocomplementemia
- Type II mixed cryoglobulins

Comments

Salient clinical, laboratory and pathologic features of the syndrome of mixed cryoglobulinemia (MC) (10) for our patient are summarized in Table 1. Salient features of her case history include:

1. A diagnosis of cutaneous vasculitis and cryoglobulinemia was only made five years after

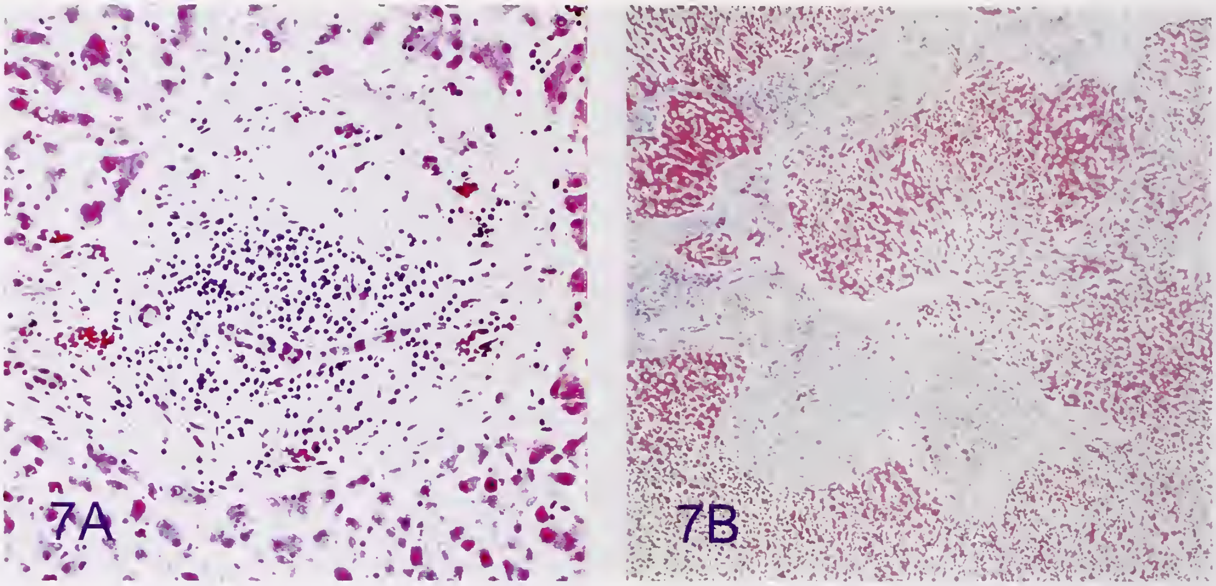

Fig. 7. Liver sections taken at autopsy: (**A**) A portal tract shows enlargement with fibrosis and a lymphoid aggregate surrounding a bile duct (H&E, 200x). (**B**) Under lower magnification, fibrous septa are seen as blue bands amid the red hepatic parenchyma, bridging adjacent portal tracts (Masson's trichrome, 20x).

the onset of symptoms, when the patient sought care for leg ulcers (Fig. 1A).

2. Sensorimotor neuropathy was clinically subtle and did not show progression on serial electrophysiologic studies.
3. HCV infection was demonstrated serologically, as well as by PCR testing of serum, isolated cryoprecipitates, peripheral blood mononuclear cells, and by RT *in situ* PCR of liver tissue. HCV infection was not due to intravenous drug abuse, co-existent HIV infection, or known prior blood transfusions. It progressed to early fibrosis over a three-year period, and there was no history of alcohol abuse.
4. There was no biochemical or virologic response to a trial of IFNα, which however had to be discontinued because of pulmonary abnormalities (Figs. 3 and 4A) that may in retrospect have been due to underlying disease.
5. It is important to carefully evaluate individual patients for underlying renal disease. In this case, proteinuria and progressive deterioration of renal function turned out to be due to hypertension, a retention cyst, and was preterminally aggravated by supervening hepatic glomerulosclerosis. There was no evidence for immune-complex glomerulonephritis or cryoglobulin deposition by immunohistology or electron microscopy.
6. B-cell proliferation was clonal on initial bone marrow examination (Fig. 6A) and evidenced in the persistent presence of an IgMκ monoclonal cryoprotein. It was also oligo- or polyclonal in the presence of mature lymphocytes, positive for both kappa and lambda light chain determinants, at multiple sites on autopsy (Fig. 6B–D).

HCV and Autoimmunity

The acute phase of viral hepatitis infections may be associated with a significant elevation in IgM levels, which in part reflects early IgM antibody responses to various viral antigens. In chronic HCV infection, a polyclonal increase in IgM may be seen, which is due in part to antibody production, now including autoantibodies, most notably IgM antiglobulins (i.e., RFs) reactive with the Fc portion of IgG. Some of these RFs form cryoprecipitable immune complexes on binding to their antigen (i.e., IgG), which may result in type II (monoclonal IgM) or type III (polyclonal IgM) mixed cryoglobulins (11 – 13).

The overall incidence of cryoglobulinemia in chronic HCV infection has ranged from 13 – 54% in different series (14 – 16). Although a correlation between the presence of cryoglobulins, duration of disease, severity of liver pathology, and the presence of extrahepatic manifestations of disease has been made, it is inexact and may be violated in individual cases. The distinction between Types II and III cryoglobulins is generally made by immunofixation analysis of isolated cryoprecipitates, looking for signature clonal Ig μ heavy chain and κ light chain bands; this type of analysis still allows for oligoclonality that might be revealed by more sensitive techniques such as two-dimensional gel electrophoresis or direct sequencing of separated heavy or light chain proteins (17). Although Type II cryoglobulins have been correlated with more severe disease, and particularly with the syndrome of mixed cryoglobulinemia (above), careful longitudinal studies to establish the evolution of a polyclonal IgM antiglobulin response to the selective V-region gene usage characteristic of monoclonal cryoprecipitable IgM RFs have yet to be carried out (18, 19).

Autoantibody, and in particular RF, activity may be seen in the course of various chronic viremias (notably Epstein-Barr), and may complicate the interpretation of these tests, which are often erroneously thought to be diagnostic of specific connective tissue diseases. In some series, chronic HCV infection, in particular, has been associated with a high incidence of other serologic indices of autoimmunity and immune-complex formation (Table 2), in most instances not correlating with overt extrahepatic disease (11, 13, 20–24).

The mechanisms responsible for the expansion of autoantibody-producing B-cells in chronic HCV infection remain conjectural. Possibilities include: (a) attenuation of dominant T-cell suppression of B-cells producing autoantibodies during chronic infection, as has been suggested for Epstein-Barr virus; (b) expansion of autoantibody-producing B-cells due to dysregulation of anti-idiotype networks; (c) molecular mimicry between viral and self-antigens; (d) direct modulation of immune responses by immune complexes or fragments of Ig (e.g., Fc) or complement components that may be generated in the course of infection; (e) dysregulation of cytokine networks skewing regulatory T-cells to a Th2 phenotype, which may be associated with enhanced humoral immune responses and autoantibody production; (f) direct infection of specific subsets of B- or T-lymphocytes and/or other mononuclear cells; and (g) host genetic factors (e.g., HLA) which may influence the ability of the host to clear virus or sustain humoral or cell-mediated immune responses.

TABLE 2

Immunologic Manifestations of Hepatitis C Infection

- IgM-containing immune complexes
- Cold-dependent activation of complement
- Rheumatoid factor (~70%)*
- Antitissue antibodies (40–50%)
- Lymphocytic sialoadenitis* (~50%)
- Anticardiolipin antibodies* (~20%)

* In most instances not associated with clinical rheumatoid arthritis or Sjögren's syndrome, and very rarely with antiphospholipid antibody syndrome

The Spectrum of Extrahepatic HCV Infection

A number of recent reviews have summarized an expanding spectrum of disorders, including several recognized rheumatic diseases (Table 3), with which HCV has been associated (25–27). Few approximate the association seen in the syndrome of MC, in which 60–80% of patients can be shown to be HCVAb and/or HCV RNA positive (28). MC, membranoproliferative glomerulonephritis, cutaneous vasculitis, and peripheral neuropathy provide overlapping syndromes in which HCV should be considered in planning diagnostic work-ups, and in which cryoglobulins may be detected in blood. In other instances, reports remain largely anecdotal or have not been uniformly confirmed. Only rarely has a defined rheumatic disease been reported to clearly follow acute HCV infection (29). Conversely, the prevalence of clinically apparent extrahepatic disease among patients chronically infected by HCV, though estimated to be less than 5% (2), has yet to be carefully delineated.

HCV and Lymphoproliferation

It has been recognized for a number of years that monoclonal mixed cryoglobulins, as well as clinical features of the syndrome of mixed cryoglobulinemia, may be associated with lymphoproliferative disorders, notably including Waldenstrom's macroglobulinemia, chronic lymphocytic

TABLE 3

HCV and Immunologic Diseases

- Autoimmune hepatitis
- Membranoproliferative glomerulonephritis
- Mixed cryoglobulinemia
- Polyarthritis
    - – rheumatoid-like
    - – adult stills disease (†)
- Polyarteritis nodosa (*)
- Sjögren's syndrome (*)
- Behçet's disease (†)
- Polymyositis (†)
- Vasculitis (†)

(*) Controversial

(†) Case Reports

leukemia, angioblastic lymphadenopathy, and non-Hodgkin's lymphoma (NHL) (30). Molecular analysis of Ig variable region sequences in some of these disorders has demonstrated selective patterns of usage that are also seen in patients with the clinical syndrome of MC (see above). At the antigenic level, selective V-region gene usage is manifest as shared idiotypes (i.e., cross-reactive idiotypes [CRIs]) that occur on both the heavy and light chains of the IgM RFs in the mixed cryoglobulins. These CRIs also occur with increased frequency in the serum of patients with chronic lymphatic leukemia (CLL) and NHL (18). A high incidence of multifocal lymphoid aggregates on bone marrow examination, often with a paratrabecular localization, that appear frequently to be immunohistologically monotypic, correlating with the clonality of Type II cryoglobulins, has been reported among MC patients (31, 32). The overall incidence of NHL among MC has been reported to be as high as 38.7% in one Italian series, virtually all HCV RNA-positive (33). By contrast, MC is rarely associated with other malignancies, notably including hepatocellular carcinoma. These observations suggest that HCV may be a linking and potentially etiologic factor for these disorders.

An increased prevalence of HCVAb and/or HCV RNA among patients with NHL was first reported in 1994 from Italy (34), where HCV and MC were known to be endemic. It was subsequently confirmed in small series from a number of different geographic regions of Italy. In an early review of the Italian reports, 434/2274 (19.1%) cases of B-cell NHL were HCV-positive, and 41.2% of those analyzed were associated with cryoglobulins (35). By contrast, HCV was not significantly associated with Hodgkin's disease or T-cell NHL. Associations with multiple myeloma or monoclonal gammopathy of undetermined significance (MGUS) have been found in some, but not all, series (36, 37). Linkage between HCV and NHL have subsequently also been reported from Japan, the United States, France and Turkey (38–41), but have not been confirmed in other series from the United Kingdom, the Netherlands, the United States and Canada (42–45).

Among patients with NHL found to be HCV-positive, more specific associations with low-grade disease, the lymphoplasmacytoid lymphoma/immunocytoma phenotype, and extranodal localization have been found (46–48). Reports of an increased prevalence of HCV among mucosa-associated lymphoid tissue (MALT) lymphomas (49), although reinforcing the concept that progression to lymphoma may be antigen-driven and oligoclonal by analogy to emerging information regarding MALT tumors associated with *Helicobacter pylori* infection (50), have not been universally confirmed (51). Conversely, as seen in the follow-up of our patient, chronic HCV infection and mixed cryoglobulinemia may manifest as clonal B-cell proliferation by flow cytometry of bone marrow, even in the absence of morphology indicative of NHL (52). More generally, NHL and HCV-infected patients without cryoglobulinemia have evidence of clonal B-cell proliferation (53), selective heavy and light chain V-region usage, and somatic hypermutation, assessed by Ig gene rearrangement and direct sequence analysis of V-region genes in patients with immunocytomas (18, 54).

The mechanisms that may be responsible for a relationship between HCV and NHL remain uncertain. A number of studies have described localization of HCV to peripheral blood mononuclear cell (PBMC) populations, both in MC patients (55, 56) (including our patient) and those with chronic HCV without cryoglobulinemia (57); specific concentration of viral RNA in CD19-positive B-cells (56, 58) and pluripotent hematopoietic CD34-positive stem cells (59) has been reported. Although these observations have been widely cited as substantiating HCV to be a lymphotropic virus, nonspecific adhesion of viral RNA and vicarious endocytosis of HCV-containing immune complexes have not been rigorously excluded as relevant mechanisms (60). Recently, specific binding between HCV envelope protein E2 and CD81, a surface marker present on several peripheral blood monocytic cell (including B-cell) populations, has been reported (61). Similarly, although positive findings have been reported for *in situ* hybridization of PBMC (62), viral RNA has not been shown to be specifically enriched in malignant lymphocytes, and the presence of replicative intermediates within selected cell populations has only been shown in limited studies (60, 63).

The possibility remains that some genotypes (e.g., 2a) (64, 65) or quasi-species of HCV may be more selectively lymphotropic (also explaining the relative lack of clinical hepatitis among the HCV-positive NHL patients) than others. Liver damage in patients with MC may reflect intrahepatic B-cell clonal expansions, and cytokine-mediated inflammatory effects of the often striking lymphocytic infiltration of liver, rather than hepatonecrosis (66, 67). Proliferating lymphocytes have been reported to be infected with HCV and to selectively express mixed cryoglobulin cross-reactive idiotype (MC CRI), reinforcing in turn an etiologic linkage between the two (66). Exactly how

HCV may in fact trigger oncogenic transformation of B-cells remains a critical issue. Of particular interest in this regard is a series of recent studies that have overexpressed HCV core protein in cell lines, and demonstrated a variety of concomitant biological effects (Table 4) that link inhibition of apoptosis and oncogenic potential (68–71). The relevance of these intriguing observations to natural infection remains to be established.

Treatment

The clinical course and outcome of the patient reported above raises several issues as to appropriate therapy targeted specifically to eradication of HCV and lymphoproliferation in this setting. These include:

1. MC may be an indolent disease, with a long survival (up to 45 years from onset in our experience) even without any treatment (30, 72).

2. Overall, renal involvement, in the form of membranoproliferative glomerulonephritis, has a negative impact on survival, though kidney disease may remain stable over long periods of time, especially when hypertension is adequately controlled (30, 72). Although proteinuria and hematuria initially suggested the possibility of glomerulonephritis in our patient, this was not corroborated pathologically.

3. Necrotizing vasculitis may be entirely cutaneous in some patients; a more bland obliterative vasculopathy has also been described (30). Although vasculitis of the vasa nervorum has been shown in some patients with neuropathy, in other instances different mechanisms (including cellular immune reactions) may result in neuronal damage (73, 74).

4. Although corticosteroids and cytotoxic agents may be effective treatments for some of the manifestations of MC, they pose a problem with regard to eradication of HCV because of the potential for elevating viral count while masking hepatic inflammation by normalizing liver function tests (75). Immunodeficient persons (e.g., co-infected by HIV) have a higher incidence of HCV viremia, higher viral titers, and in some series a higher incidence of cryoglobulinemia (76).

5. Biological efficacy of IFNα in MC may be due to its antiviral, antiproliferative or immunologic effects. The latter include upregulation of HLA antigens, direct effects on Ig production by B-cells, induction of regulatory T Helper (Th1-like) cells (associated with protective antiviral immune responses), and activation of natural killer (NK) cells (77). The importance of the antiproliferative effect may be reflected in the regression of B-cell proliferation in some patients with MC, in response to this agent (78).

6. Problems with IFNa as monotherapy for HCV infections include:

    a. Lack of response in some patients, possibly due to viral or host genetic factors. Thus, HCV genotyping as 1b in our patient may have predicted a relatively poor response to IFN based on past studies, even though 70–80% of the North American infected population are genotypes 1a/1b (79). Although she appeared not to respond clinically, or with regard to cryoglobulin quantitation or HCV copy number (Fig. 4A), it is likely that IFN was having some suppressive effects, evidenced in a redistribution of viral RNA from the cryoprecipitate to the serum supernatant (Fig. 4B), and a striking "rebound phenomenon" following discontinuance of the drug (Fig. 4A). It has previously been noted that a significant proportion of patients who start out with normal ALT levels may develop elevations in LFTs *de novo*, either during or after treatment with IFNα (80). Other host factors that have been implicated as affecting responsiveness to IFNα include expression of specific receptors in liver (81), interleukin-10 promoter polymorphisms (82), and specific major histocompatibility complex (MHC) Class II alleles (83).

    b. Uncovering of autoimmune phenomena (e.g., anti-insulin, antithyroid or antinu-

TABLE 4

Biological Properties of HCV Core Protein

- Inhibits cisplatin and c-myc-mediated apoptotic cell death
- Represses p53 transcription
- Transforms primary rat embryo fibroblasts to a tumorigenic phenotype
- Interacts with cytoplasmic tail of lymphotoxin-β receptor
- Inhibits TNF-alpha-mediated apoptosis
- Associates to cytoplasmic lipid storage droplets and ApoAII
- Inhibits Fas and tumor necrosis factor alpha-mediated apoptosis via NF-κB activation

clear antibodies) or frank autoimmune disease (e.g., lupus erythematosus) in other patients (84, 85), some of which may mimic the clinical manifestations of MC. As with our patient, one previous report has recorded lethal pulmonary vasculitis as a manifestation of MC unresponsive to IFN treatment, with evidence of a striking lymphocytic vasculopathy at postmortem (86)

c. Other toxicities (84).

d. A high rate of relapse, which may be due in part to escape of viral mutants, or quasi-species of the virus, from reservoirs in serum, liver, cryoprecipitates, or PBMC (57, 87). The escape results in turn from poor editing by the viral RNA-dependent RNA polymerase, reflected in a mutation rate of 10^{-3} to 10^{-4} base substitutions per genome site per year (88).

Plasmapheresis provides an adjunctive therapy for MC that should be combined with more specific treatment of the underlying disease, and may be complicated by rebound on discontinuance. Cryopheresis is still employed in some centers as a potentially more effective modification of this therapeutic modality (89). Alternative therapies that have been used for other forms of vasculitis, such as colchicine, antimalarials, or thalidomide, either have not been effective or remain untested. As noted above, antiviral agents, such as IFN and ribavirin, may have significant immunomodulatory effects (77, 90) that influence HCV pathology, and have been used in combination therapy with promising results as an initial treatment, for patients failing IFN alone, and in MC (91–93). Other therapies (Table 5) remain investigational (7).

Conclusions

The syndrome of MC is an interface between autoimmunity and lymphoproliferation that is significantly associated with chronic infection by HCV. The hallmark of the B-cell response in this disorder is clonality, specifically involving the IgM isotype, and measured in part by the identification of RFs that become cold-precipitable when complexed with IgG. By contrast, the peripheral blood T-cell response in this disorder appears grossly to be normal. HCV could potentially drive this process by chronic antigenic stimulation, which may undergo subtle variations over time, reflecting the virus' high mutation rate; it may also stimulate polyclonal B-cell proliferation or directly infect specific PBMC populations. In some cases, this eventuates in frank NHL, which may be demonstrated early by bone marrow examination, or become apparent after prolonged periods of infection. This outcome of chronic HCV infection appears to be distinct from the progression to fibrotic liver disease, frank cirrhosis and hepatocellular carcinoma. Eradication of virus would appear to be a desirable goal that will reduce both adverse outcomes, though a significant role for immunomodulatory effects of agents such as IFN and ribavirin has not been discounted.

TABLE 5
Investigational Therapies

- Various IFN preparations/regimens
- Ribavirin/combination therapy
- Protease/helicase inhibitors
- Antisense oligonucleotides
- Glycosylated E1/E2 complexes or recombinant capsid surrogates for vaccination
- DNA vaccines
- Adjunctive cytokine therapy

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White Coat Ceremony

To Be a Physician

Daniel W. Foster, M.D.

WHAT WE DO HERE TODAY IS SYMBOLIC. It is not of substance. It is symbol. Symbols, as philosophers understand them, have two characteristics. They are true and they point beyond themselves to that for which they stand. The symbol today is the white coat of the physician. What it points to is physicianhood, the goal of every student here, even though years away. I won't comment on the whiteness, except to say that in religious tradition white has always stood for goodness and purity. The symbol says that when I wear this coat, I cover myself and my problems and focus with absolute sincerity and integrity on my duty to heal the sick.

Sir William Osler was considered the greatest physician of this century. In 1902 he gave an address (1) which he began by saying: "I wish to bring home to your hearts certain distinctive features of our profession." This day, at the beginning, I remind you of the four characteristics about which Osler spoke, the characteristics of the physician.

First, we have a noble ancestry. "No other profession can boast of the same unbroken continuity of methods and of ideals," Osler said. We may be justly proud of the long line of true physicians going back to Hippocrates, Maimonides, Galen and Aretaeus. Of course, there have been pirates in the system — there still are — but it is the long line that is true. You are called to join it.

Second, we have a remarkable solidarity. We are men and women of all races and creeds, but one solidarity. Our solidarity is "to wrest from nature the secrets which have perplexed philosophers in all ages, to track to their sources the causes of disease, to correlate the vast stores of knowledge, that they may be quickly available for the prevention and cure of disease — these are our ambitions," he said.

Third, we have a progressive character. We change and change constantly as science brings new information to bear. A corollary of that is that a physician is a life[-long] student. We understand that medical education is not an event, but a process. Osler: "In the unloading of old formulae and in the substitution of the scientific spirit of free enquiry for cast-iron dogmas, we see promise of still greater achievement and a more glorious future." You must be life students. As a personal testimony, I study more now than I did in medical school. And that is not a burden. It is a joy.

Fourth, we have a singular benevolence. True physicians are not only competent and knowledgeable, they are kind. Osler said that medicine has reduced the average sum of human suffering "in a way to make the angels rejoice."

These, then, are the characteristics of true physicians: to keep the noble heritage, to fight disease, to be constantly progressive, to remain always benevolent. They should become your goal this day. The great Lister, discoverer of antisepsis, summarized the profession this way in a graduation address (2) at Edinburgh: "It is our proud office to attend the fleshly tabernacle of the immortal spirit, and our path, if rightly followed, will be guided by truth unfettered and love unfeigned. In this noble and holy calling," he said, "I wish you all Godspeed."

We don't talk that way today, but what he is saying is that this is a pretty nifty profession: to

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Key Words: White Coat Ceremony, Osler, Lister, Maimonides.

seek truth in disinterested fashion, which is our science, and to practice unfaked love, which we usually call compassion.

One other thing. This life is sometimes hard. You will have hard times in your studies. One is fairly often tired, both as a student and as a practitioner. It is hard also because we do not always win the battle against disease and have to participate in suffering and death. One of my best friends and colleagues on the faculty has a metastatic colon cancer. The outcome is uncertain, but I think it will be easier for him because I will accompany him on the journey. And that will be a privilege. A hard privilege, but a privilege. That's okay, because it has always been hard for the long line about which I have spoken and which I hope you will join.

I thought I might illustrate the hardness and the willingness to bear it with an eloquent essay written by Prad Ramamirtham, a recent graduate of our residency program. He gave it to me shortly before he left. He titled it, "*Why I go up on the roof.*"

> Swimming day in day out in the murky depths of human despair can leave one despondent. It raises daily, sometimes hourly, the age-old question — Why? Such is the life of a resident in a busy county hospital. Bearing witness to the folly of Pandora's curiosity, watching disease slither in its naked form with the stench of misery filling every crevice of the Emergency Room can leave a doctor's heart numb, his hands cold, his head calculating. We seek refuge in the sanctuary of Science; in the disease process. Through timeless practice we have become experts at separating a patient from his illness. Rule him out. Tube him. Culture her up and start broad spectrums. She needs spun[1]. We have some Motrin for you, sir. So I tread calmly for hours as this social genocide gathers at our hospital doors — a holocaust of the poor and indigent — until finally, I, too, am affected.
>
> It is at these times that I make my pilgrimage up the north elevators to the tenth floor. Clambering up the final few stairwells, I carefully push [open] the metal door to let the final streaks of daylight flicker on the dimly lit steps. Stepping out onto the roof I am greeted by the western apricot sky with its hues of green and blue and orange and red. Airplanes gently rise from the nearby airport, offering the soft silhouette of their underbellies as they turn to chase the last light of the sun. To the east the nightcalls begin from downtown Dallas, with the glass and concrete walls of the city giving testimony to man's ascension to power. After a few silent moments I can feel the vibes of the city. The collective vibe from every little household, each with its own pain and glory. I open up and let it seep into every pore, and slowly again I feel a part of humanity. This is why I go up on the roof.
>
> My beeper goes off, and so I leave the green glow of the Heritage Building and the glittering ball of Reunion Tower guarding the chasm of Interstate 35 and return to the E.R. to see my next admission. It's a 35-year-old white man with a CD4 count of nothing. He's got a fever, he looks scared, he looks sick. I take a deep breath and in a few seconds my heart starts to soften, my hands warm, my head's still ticking away at a million miles an hour. An invisible tear wells up in the corner of my eye as I begin, "It's going to be okay, sir. What brought you to the hospital today?"

Well, what I have tried to say is that this white coat is a symbol of that which I hope you will be — a true physician. You can mess it up. You can throw it away. You can even become a pirate. But don't. You will miss out on something great if you do. Something noble, Osler said.

I mentioned earlier the name of Moses Maimonides, the great Jewish theologian/physician of the 12th century. There is a prayer that is attributed to him. Like many ancient documents, there are some who believe that he did not actually write it (3). But that does not matter. What matters is the message therein. The same message as Osler's. The message of Prad Ramamirtham. The message is that it is a noble profession, that there is a need for perpetual study, that the demands for mercy and compassion are constant and uncompromisable. This is the prayer:

> I begin once more my daily work. Be thou with me, Almighty, Father of Mercy, in all my efforts to heal the sick. For without thee, man is but a helpless creature. Grant that I may be filled with love for my art and for my fellow man. May the thirst for gain and the desire for fame be from my heart. For these are the enemies of Pity and the ministers of Hate.

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[1] Resident shorthand for an hematocrit.

> Grant that I may be able to devote myself body and soul to the children who suffer from pain.
>
> Preserve my strength, that I may be able to restore the strength of the rich and the poor, the good and the bad, the friend and the foe. Let me see in the sufferer the man alone. When wiser men teach me, let me be humble to learn; for the mind of man is so puny, and the art of healing is so vast. But when fools are ready to advise me or find fault with me, let me not listen to their folly. Let me be intent upon one thing, O Father of Mercy, to be always merciful to thy suffering children.
>
> May there never arise in me the notion that I know enough, but give me strength and leisure and zeal to enlarge my knowledge. Our work is great, and the mind of man presses forward forever. Thou has chosen me in thy grace, to watch over the life and death of thy creatures. I am about to fulfill my duties. Guide me in this immense work so that it may be of avail.

I find that prayer beautiful. I hope you do too. I will not be here to watch or participate in your education. I know it will be safe, because I know and trust the leadership of your school. As a consequence I will leave with the same single word used by Lister at Edinburgh: Godspeed.

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The Bell Commission:

Ethical Implications for the Training of Physicians

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Abstract

In 1989, the New York State Legislature enacted New York State Code 405 in response to the death of a patient in a New York City hospital. Code 405 was the culmination of a report (the Bell Commission Report) that implicated the training of residents as part of the problem leading to that tragic death. This paper explores the consequences of the regulatory changes in physician training.

The sleep deprivation of house officers was considered a major issue requiring correction. There is little evidence to support the claim that sleep deprivation is a serious cause of medical misadventures. Nevertheless, the changes in house officers' working hours and responsibilities have profound implications. Changes in the time allotted to teaching, the ability to learn from patients admitted after a shift is over, and the increasing loss of continuity, all may have a negative impact on physician training. It is not clear that trainees are being realistically prepared for the actual practice of medicine — physicians often work extended hours.

The most serious concern that has been raised is the loss of professionalism by physicians. Residents are now viewing themselves as hourly workers, and the State has intervened in an area of training formerly left to the profession to manage. We are now training doctors in New York State who will be comfortable working in an hourly wage setting, but not in the traditional practice of medicine as it has been in the United States during this century. We are concerned that this may sever the bond between doctor and patient — a bond that has been the bedrock of our conception of a physician.

Key Words: Bell Commission, residents, training, bioethics, professionalism.

In 1989, the New York State Legislature enacted New York State Code 405 in response to the tragic death of Libby Zion at New York Hospital. The enactment was the end result of a wide-ranging investigation by the State Department of Health, the Bell Commission, the court system, and the newspapers, leading to the conclusion that the manner of training residents was somehow part of the problem. Besides an immediate flurry of publications in the popular press, some attention was given to these new rules in the academic literature, both medical and bioethical. In this paper, we wish to explore what we view as the profoundly troubling consequences of these changes.

One of the major issues considered by the Bell Commission was the deleterious effect on patients of house officers' sleep deprivation. Although it was not clear that sleep deprivation was a major cause of medical misadventures generally, the members of the Bell Commission saw this as an opportunity to correct what they perceived to be a problem in the training of physicians. Among their mandates was the stipulation that physician house staff must not work more than 24 consecutive hours, must have no less than 8 non-working hours between shifts, and must not work more than 80 hours per week. These recommendations are not conclusively supported, however, by evidence in the sleep literature. While a meta-analysis of nineteen studies has demonstrated both decreased performance on standard tests of cognitive function and altered mood with sleep-deprivation (1), Storer and col-

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leagues (2), using board examination questions to test cognition and patient care tasks to test coordination, demonstrated no deleterious effects of sleep-deprivation in pediatric residents.

Issues of proper supervision by attending physicians were also raised in the Bell Commission deliberations, and rules about the availability of attending staff were mandated. These were far less proscriptive. To our knowledge, nothing has been written concerning the impact of the changes in attending physician supervision, and we have chosen, in this paper, to focus primarily on the resident physician rules.

In order to examine the short- and long-term implications of the Bell Commission, we need to examine the goals of house officer training from the point of view of the teacher. Then we can determine whether the Bell Commission regulations allow us to realize them. We must then also examine whether the resident physician rules substantially change the doctors who are trained under them, and if these new doctors can be effective in providing health care that meets the goals of their training. This assessment involves two interrelated facets. The first relates to the bottom line, i.e., will we have competent physicians to care for patients? The second relates to the broader issue of professionalism. We shall deal with both facets in this paper.

Let us begin with some generalizations about the nature and purpose of training interns and residents. First and foremost, we should want to maximize learning. In medical training, learning derives from many activities: reading, lectures, hands-on experience, observing, etc. Bell Commission guidelines were initially interpreted as allowing trainees to attend teaching sessions after the 24-hour limit, but recent audits of New York City programs have thrown this aspect of the regulations into a state of confusion. If it is acceptable to go to lectures after the 24-hour limit, then the message being sent to residents is that didactic learning is of less importance than patient-centered learning. We have seen no evidence to suggest that the Bell Commission has improved learning by residents — if anything, we submit that there has been a negative effect.

In a medical setting, maximizing learning requires, in a limited time, exposing our trainees to as many patients and diseases as possible. There is no question that the most skilled physicians are those who have been exposed to and cared for the widest range of patients. Learning from lectures and texts will never replace the reality of the patient encounter. In some cases, a trainee may have seen a wide enough range of patients with a particular problem to be competent in their management; in other cases, there are truly enough variations and permutations to make critical more clinical exposure. Should the trainee never go home? Obviously that is not a practical solution. But decisions about when to leave the hospital or clinic should be left to the individual, who is probably in the best situation to judge.

Learning clinical medicine involves more than single or multiple exposures to diseases. It requires exposure to the continuity of individual patients' care, through illnesses and life experiences. The more of this we see, the more we learn. While the Bell Commission opines that patient care would be improved with discontinuous care, the literature is more ambiguous on this issue. Residents have reported concerns about developing a shift-work mentality and an inability to provide continuity of care (3, 4). Studies of the effects of post-call transfer of resident responsibility have demonstrated deleterious effects on length of stay and test ordering, and an increase in medical complications (5, 6). Gottlieb, however, developed a scheduling model designed to reduce sleep-deprivation and improve continuity, and demonstrated decrease in lab test ordering and length of stay (7).

An additional goal for graduate medical education should be to adequately prepare trainees for the careers they will enter. Fifty-seven percent of 1998 graduates of New York State Medical training programs reported a plan to enter patient care/clinical practice (8). Yedidia (9) has argued that the Bell Commission regulations foster shared decision making and collective responsibility, which may conflict with the autonomy and individual responsibility that were traditionally taught and that remain integral to the life of an attending physician. In addition, the new regulations were among several factors that promoted an expansion of training positions in New York State (10). Our teaching goals should include preparing residents for the current job market, and we are concerned that 43% of those responding to the above exit survey reported difficulty finding a job with which they were satisfied; 44% reported few, very few or no jobs within fifty miles of their training site.

An essential component of all medical school teaching is the apprenticeship role of the trainee. Interns and residents learn from their mentors. They watch, assist, and interact with senior physicians caring for patients. For excellence in medical education, the supervisor is the teacher, the model, the ideal to which the trainee aspires. The more we make this a reality, the more successful training will be. The Bell Commission regulations seem to recognize the importance of this apprenticeship when they mandate increased supervision. For the Bell Commission, however, the supervisor is there primarily to prevent mistakes. While these two functions are not at all mutually exclusive, too little thought and effort have occurred to meld them into one.

We are also concerned that the Bell Commission regulations are part of a disturbing movement accelerating the loss of the professionalism of physicians. James Gustafson speaks of professions as "callings" — they involve motivation (including moral motives) and a vision of the ends to be served (11). For the trainee, the motivation must be to learn how to become the best physician possible. Part of the learning is through caring for patients, part is through didactic learning. At no previous time in the history of physician training was there a concept of the trainee as an hourly worker. A resident aspired to train at the best program for learning, not the one with the easiest call schedule or fewest admissions at night. At the end of internship, the physician felt (and generally was) remarkably knowledgeable, proud of an ability to manage most illnesses that most patients were likely to have. While we all knew there was still much to learn, it was certainly true that we had acquired a tremendous amount of knowledge and skill.

While professions traditionally controlled training of new members, now the "State" has become a significant force in this training. In a not too subtle way, the Bell Commission rules tell house officers that they are members of the workforce, and that they should think of their labor contract in terms of hours, wages, vacations, and protocols. Instead of choosing obligation over self-interest (another definition of professionalism), our trainees are taught to reverse these priorities. We quantify their work and put twenty-four hour limits in place.

In effect, this revises the very concept of intern and resident. Never before did the educators (the medical school faculty and clinical attending physicians) openly plan for a way to care for patients without interns and residents. It is common now for faculty to sit in meetings, nodding their heads knowingly, when it is said that the house staff are of little value to the clinical service. To make matters worse, managed care companies and state and federal reimbursement programs pay only the most minimal lip-service to the value of training new physicians.

While the Association of American Medical Colleges has endorsed the 80-hour limit as consistent with the goals of graduate medical education (12), we propose that the Bell Commission Regulations are part of a fundamental change in our training, and that its implicit transformation of the concept of who and what a physician is has significant ethical implications. By interfering with optimal training as we have defined it, these regulations place patients at as great a risk from lack of professional commitment as any perceived risk from sleepy interns. This is not an immediate risk, but clearly a risk for the future. We are assuring that only rare physicians will recognize their fiduciary role as the professional who is always there for the patient. The State has said, "Go home. Someone else can do it." We have now institutionally sanctioned behavior that used to arouse guilt and remorse. We have said that it's fine to leave a sick patient. Someone else will deliver care. Even if that was always, as least in part, the reality, it was not our ethos. The interns and residents still feel wrong about leaving. A few stay way past the scheduled hour, but many do not. Some say their own personal lives are more important. Maybe that is true. But this represents a very serious change in the professional attitude doctors have traditionally expounded.

The proponents of the Bell Commission Regulations have answers to these criticisms. They say we can train people in other ways. Work around the time problem. Hire others to care for most of the patients. They are missing the point. No one would argue that we need more senior physicians around. That could only improve education as we have defined it. But that is not really the issue. The loss of the relationship between the trainee and the direct, continuous learning from patients presents the most serious attack on the traditions of medicine. If we look at the training of physicians using the framework of raising our children, we can reach the same conclusions that Erik Erikson reached in his seminal publication (13). He stated that "small differences in child training are of lasting and sometimes fatal significance in differentiating a people's image of the world, their sense of decency, and their sense of identity." We are now training doctors in New York State who will be comfortable working in the hourly-wage setting but not in the traditional practice of medicine as it has been performed in the United States up to now. We are laying the groundwork for severing the bonds between doctor and patient.

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The Ethics of Placebo Prescribing

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Abstract

The prescribing of placebos brings into focus the practice of being truthful to patients. The term "placebo" has a generally pejorative connotation in medicine, although the Latin means "I shall please." More recently, the definition of "placebo" has expanded to include "medication without proven pharmacological activity." Yet it is known that the use of placebos often leads to substantial improvement. The effectiveness of placebos is a challenging and troubling issue for physicians. **Key Words:** Ethics, placebos.

WHEN I THINK OF THE CHANGES that have occurred in the half century since I entered medical school, three seem especially important: the development of pharmacologically active drugs (I remember prescribing "tonics" frequently in my early years); the development of statistically significant trials; and perhaps equally important, the demand by patients to be given truthful information about their health status so that they can be fully involved in decisions about their care. This is not to say that one should overwhelm patients with this information — one may be "economical with the truth," to quote a famous phrase used by the UK attorney general in the Peter Wright spy trial — but on the whole, one should aim at being truthful so that patients can make informed choices.

The prescribing of placebos brings these three areas into sharp focus, and this is what I want to deal with in this paper. At the same time, I want to touch on the view held by many of those practicing orthodox medicine, that complementary medicine is a form of organized (or perhaps disorganized) placebo prescribing and, therefore, somewhat immoral.

First a case history:

A thirty-year-old farmer was giving his three-year-old son a ride on his tractor, when the boy fell off. He was run over and killed. The mother had told the father that she thought it unsafe for the boy to ride on the tractor, so the father not only lost his son, for which he felt responsible, but found his marriage in trouble.

The father developed severe backache, which did not respond to ordinary analgesics, or to suggestions that the cause was psychosomatic. I was called out one night to see him. He was unable to move due to spasm of his back muscles, and I could think of no alternative, in the acute situation, to giving him an injection of meperidine. The next night the same thing happened, and by the third night I was losing sleep and getting worried about the prospects — the patient's and mine!

I took him into our local community hospital and requested that the nurses give meperidine during the night, if required. After the first night I decided that I would have to change course, so I prescribed distilled water by injection if he had pain in the night again. The water worked, and I was then faced with what to do next.

I decided to tell him the truth — that he had been given an injection of water in the night and that this had relieved the pain. Fortunately, he accepted my subterfuge and we were then able to start dealing with the

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backache as a psychological rather than a physical problem.

I was left with an uncomfortable feeling that I had deceived my patient. However uncertain I was as to what category the treatment belonged to, I felt that the water had been used as a placebo, but that it was also a rational form of treatment in this particular case. It is this dilemma which led me into thinking about placebos in general.

"Placebo" is Latin for "I shall please," and in medicine it has a generally pejorative connotation, suggesting that it is something given *to please rather than to benefit* the patient. More recently, a lack of proven pharmacological activity has become part of the definition as well. This usage carries with it a suggestion of deception. Yet we know that in placebo-controlled trials of drugs in patients with depressive illnesses, asthma and hypertension, the patients treated with placebos often improve substantially. Thus, the very effectiveness of placebos is both troubling and challenging to us as rational doctors.

Whenever doctors interact with patients, the event has an effect on both parties. Michael Balint coined the concept of "the doctor as drug" and described this effect as part of the doctor's therapeutic armamentarium (1). So should we consider this a placebo effect? I think not. Any person talking to a friend, or any patient talking to a trusted doctor, may derive benefit from the interaction. This is really the world of counseling and psychotherapy. There is a continuum between, at one end, listening and supporting someone, and at the other end, psychotherapy. We know that such interactions can be of benefit — and also, of course, can do harm. In other words, they have proven effects.

If we accept this restriction on the use of the word "placebo," we are left with the placebo effect as being related to an intervention, usually the prescription of an oral agent. This fits in with the *Oxford English Dictionary* definition of placebo as "a 'medicine' given more to please than to benefit a patient." But this definition will not suffice, because, as I mentioned before, in placebo-controlled, randomly allocated clinical trials, placebos do work.

Is a placebo then just a possibly effective intervention which has not been proven by scientific method such as a randomized controlled trial (RCT)? Maybe we should start by looking further at what a placebo effect is (2).

Trying to define the placebo effect on an individual basis is impossible. Too many variables confuse the picture — in particular, the effect of the doctor-patient interaction.
On a more statistically valid basis, the placebo effect could be defined as the difference in outcome between a placebo-treated group and an untreated control group in a controlled experiment, e.g., an RCT.

If we accept that a placebo does have an effect, then why, if some interventions are always less effective than others, should one intervention be labeled "placebo" and another "active"? In other words, doesn't the fact that a placebo is better than no treatment at all make the placebo an active treatment?

This leads to a definition such as "a placebo is an intervention which is believed to lack a specific effect on the disease, but which is better than no intervention."

This definition takes an important step forward by including the concept of "belief" rather than knowledge, and belief in a treatment by doctor/therapist/practitioner or above all patient is what placebo effect is about. But what does "specific" mean? Does "specific" in the phrase "specific effect" invariably mean that there is scientific evidence, or even a theory to explain a mechanism of action? We do not know the mode of action of some active treatments which we commonly use, such as lithium for depression. And complementary practitioners do claim to have theories for the mode of action of systems like homeopathy, which may rely on unproved "vibrations" of molecules for their effect. It may be that our labeling of such "alternative" or "complementary" explanatory systems as placebo effects is presumptuous. And it may be that some treatments which we now label as "placebo effects" will be proved to be of benefit and their designations will have to be changed. Had the effect of foxglove extract on heart failure been discovered now, it would presumably have had to go through this acceptance process. Many people consider that ginseng increases general well-being as well as sexual potency, but most doctors would label this a placebo effect. Were this effect ever to be proven by a properly controlled trial, the status of ginseng would change.

Perhaps we have taken this search for a definition far enough. We are left with placebos as being effective for some conditions and for which belief in their efficacy is important.

Turning to my field of general practice, the normal progression of events taught to medical students — "history → diagnosis → treatment" — is often impossible to follow. Several studies have shown that for 40–60% of general practice patients in the UK, no firm diagnosis can be made (3). Where we are unable to make a diagnosis, we have to move directly from history to treatment. And when the diagnosis is in doubt, there is a much greater likelihood of doctors, not only general practitioners, giving treatment which has no proven beneficial effect and may act only as a placebo. A problem here is that the apparent success of a treatment may mislead the doctor into thinking that the diagnosis was correct and the treatment specifically effective. Yet this may not be true (3). This phenomenon has been labeled "the therapeutic illusion" by K.B. Thomas (3) and may result in unethical consequences. The use of antibiotics in viral sore throats is an example. The patient gets better. The issue here is — does the doctor believe the antibiotic to be effective? — in which case, he has not read the results of trials. Or is he using the antibiotic as a placebo? For either reason, that is, whether the doctor believes the antibiotic to be effective in this situation, or prescribes the antibiotic as a placebo, it would be unethical even if the patient suffers no harm when colonies of resistant bacteria multiply.

It appears that the placebo effect is often used unwittingly, both in general practice and medicine in general. What about the deliberate use of placebos? Should we, as in the case that I outlined earlier, prescribe drugs or procedures which we know are of no specific value if the evidence indicates they are not harmful? In 1970, a British medical authority (4) took doctors to task for "failing to make effective use of a considerable body of scientific evidence on the placebo effect. . . . There must be occasions when an appropriately prescribed placebo will be less harmful and perhaps more beneficial than a complex and incompletely understood drug."

I consider, with Brown (5), that if doctors "can see placebos — like many other conventional drugs — as broadly effective therapies, whose mechanisms are not completely understood and which tend to be more effective for some conditions than others (and in some people more than others), they can offer placebos both honestly and as plausible treatments."

We know, for instance, that in people with hypertension, if we take their pressure regularly for a week or two, the blood pressure often comes down without any treatment. This is commonly ascribed to initial "white coat hypertension." Work done in the early 1990s by Materson at the Veterans Affairs Medical Center in Miami (quoted, but without reference, in Brown [5]) showed that at least 20% of observed patients achieved normal blood pressure after several weeks of taking placebos. I am not sure how these two groups overlap, but it would seem reasonable to say to patients after an initial period of observation that, in treating their hypertension, there are several options. One of these is to take a tablet which has no known active ingredient, but has been found in some 20% of patients to bring the blood pressure down to normal levels; the advantage of this line of treatment is that it has no side effects. If, after a while, the blood pressure is still raised, other treatments can be tried.

There is evidence that placebos seem to work more effectively in patients who are anxious and of dependent personality (6), so it would not seem irrational to try to tailor the treatment to the personality of the patient — something we often do both with drug use and with referrals — and this could include the use of placebos.

The large number of people who consult "alternative" or "complementary" practitioners of all kinds probably do so in part because such practitioners spend more time with their clients and have no hesitation in using the "doctor as drug" effect described by Balint (1) and to which I have already referred. If we accept the power and ethical use of placebos, we can become less judgmental about these practitioners, appreciating that many of their treatments are successful because of the placebo effect in its widest form. That does not mean that we have to accept the bizarre theories that they sometimes use to explain the rationale of their treatments.

Disease is defined as an abnormal state of the body, e.g., hyperglycemia in diabetes, a broken arm or a chest infection. Illness, on the other hand, the feeling of being unwell, is what brings patients to doctors. This is what people have when suffering from a disease, but also, as I have explained, when they have a condition whose cause we cannot explain. And illness is what doctors have to treat, whether by curing a disease with a specific remedy or by other means, such as using the "doctor as drug" effect, or using a placebo.

Our reluctance to use the placebo effect intentionally probably stems from the feeling that we are deceiving our patients. Going back to the case history I related at the beginning, what I was trying to do was prove to my patient that his pain was psychological and not physical in origin, and the deception involved in using a placebo effect was what had troubled me. On the other hand, if we tell our patients — if I had told my patient — that a remedy which has no proven therapeutic effect is being prescribed, its effectiveness is likely to be diminished. I am sure that would have been the case with my grieving farmer. So my problem with him was with the deceit involved, rather than with the use of a placebo. A paradox, indeed, but in this case about the ethics of deceit to further a therapeutic end, and not about the ethics of prescribing placebos — in other words, do ends justify means?

When I was discussing this paper with a friend who was a registrar of mine some 15 years ago, he reminded me that I had at one time said to him that it is whether the patient gets better that matters, not the treatment used. Perhaps I should have considered telling my patient in advance that I wanted to use a different pain reliever than meperidine (knowing that what I intended to use was a placebo). But I wonder if the different medicine would have relieved the patient's pain.

With the above reservation, I suggest that one can retain one's honesty and remain truthful with patients. In the final analysis, treatment, including the use of placebos, is a means to enhancing the well-being of the patient.

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Genetic Testing:

A Physician's Perspective

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Abstract

Progress in DNA diagnostics has been extremely rapid. We sought to determine attitudes, awareness, and knowledge of genetic testing by physicians affiliated with the Mount Sinai Medical Center.

We surveyed 363 physicians within whose fields genetic testing for various diseases and disorders exist. Physicians' awareness of and opinions regarding testing, attitudes toward counseling, knowledge of the field, and interest in further education were assessed. Three hundred forty-one (341) physicians were determined to be eligible for the study and, of these, 89 (26%) returned completed surveys.

Of the respondents, 71% rated their knowledge of genetics and genetic testing as "fair" to "poor"; only 37% read articles concerning genetic testing on a regular basis. Physician awareness of currently available testing produced a bell-shaped distribution. Knowledge regarding Mendelian genetics yielded a bimodal distribution, and knowledge reflecting an understanding of the mechanics behind genetic testing produced a bell-like curve, skewed to the right. Those who identified themselves as practicing within an "academic" setting scored significantly higher on the Mendelian genetics and testing mechanics sections than those practicing in a "private" setting. Ninety-eight percent (98%) of the physicians said they would refer their patients to a genetic counselor. Although 91% of the respondents were aware of the existence of genetic counseling services, only 71% were aware of the services available at major New York medical centers. Of those aware of counseling services, 53% had referred a patient to them, and 83% of those who referred were "mostly" to "very" satisfied with the counseling. Ninety-five percent (95%) of the physicians believed that the doctor, among others, has the responsibility to counsel patients about genetic testing, yet only 51% felt that they had the time. No statistically significant preference was found concerning the methods for gaining further education or information about genetic testing.

Further education for physicians is required in order for them to accurately convey the risks and benefits of genetic testing to their patients. Furthermore, awareness of the counseling services available within the New York area needs to be heightened in order to provide physicians and patients with the specific services they desire. The most efficient and effective methods for providing information and for heightening awareness need to be determined through additional research. **Key Words:** Genetic testing, genetic counseling, physician knowledge.

After a decade of research, the international Human Genome Project is turning the idea of mapping the 80,000 to 100,000 genes which compose the human genome into a reality (1). With such information, geneticists will be able to identify, map, and sequence genes specific to or associated with numerous diseases, potentially leading to the development of genetic tests for these diseases (1). Testing has already become commercially available to physicians for a variety of cancers and single gene disorders (e.g., colon cancer and cystic fibrosis), and more tests are currently in development (2, 3). A proper understanding of the test results, however, is essential not only for making an accurate clinical diagnosis, but also for counseling the patient, who must clearly understand and prepare for the potential consequences of the results. The field of genetic testing has begun to change the practice of medicine substantially, as patients at risk for certain diseases can be identified well before clinical signs and symptoms manifest themselves. Furthermore, current definitions of "standard of care" and "duty" to one's patients and their families must be redefined in light of the new information this technology provides (4).

Only recently have studies been carried out to assess the opinions, awareness, and knowledge currently held by a variety of physicians regarding genetic testing (3, 5–8). Only with the data gained from such studies can physicians' strengths and shortcomings in this area be ascertained. Then, new information can be distributed to them in an optimal manner, to prepare them for

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the constantly evolving and ever-growing emphasis on genetic technology in medicine. This paper hopes to present such data as it relates to the physicians who practice at the Mount Sinai Medical Center and its affiliates.

Methods

Subjects

Physicians were identified through lists obtained from their various departments. These lists represent physicians practicing at the time of the study, at either the Mount Sinai Hospital or an affiliate, when applicable. Departments were chosen if they dealt with diseases for which genetic testing was currently available. Three hundred sixty-three (363) physicians were initially identified from the departments of Neurology (n = 84, 23% of those surveyed), Pulmonary Medicine (n = 13, 4%), Geriatrics (n = 33, 9%), Cardiology (n = 36, 10%), Oncology (n = 19, 5%), Gastroenterology (n = 52, 14%), Primary Care (n = 29, 8%), and Obstetrics and Gynecology (OB/GYN) (n = 97, 27%). All identified physicians were surveyed. Respondents were assured of the anonymity of their responses.

Survey

The survey consisted of 5 sections: (1) demographic information about the physicians surveyed, (2) awareness of and attitudes toward genetic testing, (3) opinions regarding genetic counseling, (4) knowledge regarding Mendelian genetics and interpretation of genetic test results, and (5) interest in learning more about genetic testing and counseling. Space on the questionnaire was provided for the physicians to comment on their responses. Multiple choice questions and Likert response formats were used to obtain the requested information. Responses were not mutually exclusive and, therefore, some questions allowed for more than one response. The survey is available upon request.

Members of the Department of Human Genetics at Mount Sinai critically reviewed the survey to verify content validity and ensure correct keying of knowledge questions. In August of 1996, the surveys were distributed to the 363 physicians. Prepaid, pre-addressed return envelopes were included with the surveys, but no incentives for completing the survey were offered. A second mailing of the instrument was sent out 8 weeks later. Due to the anonymous nature of the study, all physicians received a second survey and were asked not to return a new survey if they had replied to the initial mailing.

Analysis

Calculations were performed using Stata versions 5.0 and 6.0 (Stata Corp., College Station, TX). Comparisons between groups were made using analysis of variance when the dependent variable had a reasonably normal distribution. Comparisons between groups of variables with skewed distribution were made using the Mann-Whitney U-Test. Correlations between variables were assessed using the Spearman or Pearson correlation coefficients for ordinal and interval-level measures, respectively. When searching for comparisons between the "academic" and "private practice" groups, we excluded from those analyses physicians who failed to identify themselves as exclusively in either group (11 of 86 respondents provided either multiple responses or "other").

Results

Of the 363 physicians initially surveyed, 91 (25%) returned surveys. Not all respondents answered every question. Twenty-two (22) of the 363 physicians were deemed ineligible for the study due to: (1) old or incorrect mailing address for which a new address was unavailable, (2) little patient contact (e.g., mostly research oriented) as noted on the returned surveys, or (3) inability to complete the survey due to unforeseeable events (e.g., death). Therefore, 89 (26%) returned surveys from the 341 eligible physicians were utilized for our analysis.

Demographics

The mean age of those surveyed was 50, with the majority of respondents being male (74%). Of 88 respondents who answered the question, 28 (32%) had received information regarding genetic testing from commercial companies. A full breakdown of the results is found in Table 1.

Education

Of the 89 respondents, 51 (57%) had taken a formal course in genetics at some point during their training, with 44 (86%) of those having taken a course in medical school. Time since completion of medical training was found to be a significant indicator of whether one had taken a formal course (p = 0.0006). Those doctors who

Table 1
Demographic Data of Responding Physicians

Age: n	Range (yrs)	Mean (yrs)
82	30–82	50 ± 13

COT: n	Range (yrs)
14	0–5
19	6–10
22	11–20
15	21–30
16	31+
Total: 86	Mean: 18 ± 13

Sex: n = 86	
Male:	64 (74)*
Female:	22 (26)

Professional Activity	n	Specialty	n	(%) Response Rate Within Each Field
Private:		Cardiology	6	(16)*
Primary Care	7	Geriatrics	8	(24)
Specialist	29	Gastroenterology	12	(23)
Academic:		Neurology	14	(16)
Primary Care	11	OB/GYN	14	(14)
Specialist	31	Oncology	2	(11)
Multiple°:	8	Pulmonary	1	(8)
Other†:	3	Other		
Total:	89	No Response	8	
		Total:	67	

Received information regarding genetic tests: n = 88	
Yes:	28 (32)
No:	60 (68)

* Numbers within parentheses represent percentage of those responding

COT = Years since completion of training

° Multiple: These physicians identified themselves in more than one of the professional categories; 7 of 8 identified themselves as specialists + an additional category and were included when determining respondent's specialty.

† Other: These physicians were not used when analyzing "academic" and "private" groups.

Table 2
Educational Exposure

Have taken a formal course in genetics: n = 89	
Yes:	51 (57)*
No:	38 (43)

Stage of Training°:	n = 51
Medical School:	44 (86)
Residency:	2 (4)
Other:	10 (20)

Read articles regarding testing on a regular basis: n = 89	
Yes:	33 (37)
No:	56 (63)

Source°:	n = 33
Journals:	31 (94)
Newspaper:	15 (45)
Other:	6 (18)

* Numbers within parentheses represent percentage of respondents.

° More than one response allowed for the question.

had taken a course had completed training more recently (mean 13.7 years) than those who had not (mean 24.2 years). Only 33 (37%) of the 89 respondents, however, were currently reading articles concerning genetic testing, with journals being the most common source, as seen in Table 2.

Self-Assessment

When asked how they would rate their knowledge about genetics and genetic testing, using a 4-point scale (1 = excellent, 4 = poor), 25 (29%) of the 87 respondents to this question rated it as excellent-to-good, while 62 (71%) rated it as fair-to-poor. Those physicians who had taken a formal course in genetics rated their knowledge higher than those who had not (mean of 2.7 vs. 3.2; $p = 0.01$), as did those who stated that they currently read articles regarding genetic testing (2.4 vs. 3.2; $p < 0.0005$). There was no statistically significant difference between "academic" and "private practice" physicians as to how they rated their knowledge. Years since completion of training also was not associated with self-rated knowledge.

Attitudes and Opinions Toward Testing

Using a 5-point scale, physicians were able to express their opinions about ordering genetic tests for various scenarios. These results are found in Table 3. While screening targeted populations for the identification of carriers of autosomal recessive disorders like Tay-Sachs was largely agreeable to physicians (81% agreed or strongly agreed), screening populations for carriers of similar disorders for the purpose of employability or health insurance coverage was found to be disagreeable (95%). Other scenarios, however, were not as easily delineated. Ordering prenatal testing of fetuses for an untreatable disease which would not manifest itself until later in life was agreeable to 44% of the respondents and disagreeable to 40%.

Knowledge

Three categories of knowledge were assessed through our survey. The awareness of genetic tests available at the time of survey distribution (KN1) was determined utilizing the 12 disorders seen in Table 4. Overall, the results yielded a

Table 3

Physician Attitudes Regarding Genetic Testing

	Strongly Agree	Agree	Neither	Disagree	Strongly Disagree	n
A.	35 (41)*	37 (44)	7 (8)	1 (1)	5 (6)	85
B.	4 (4)	18 (22)	19 (23)	22 (27)	20 (24)	83
C.	17 (20)	25 (30)	14 (17)	18 (21)	10 (12)	84
D.	12 (14)	22 (26)	14 (17)	26 (31)	10 (12)	84
E.	34 (40)	35 (41)	6 (7)	6 (7)	4 (5)	85
F.	1 (1)	1 (1)	2 (2)	10 (12)	69 (83)	83
G.	7 (8)	9 (11)	11 (13)	26 (31)	31 (37)	84
H.	16 (19)	18 (21)	13 (15)	19 (23)	18 (21)	84
I.	27 (32)	28 (33)	11 (13)	10 (12)	9 (11)	85
J.	16 (19)	17 (20)	18 (22)	19 (23)	13 (16)	83

* Numbers within parentheses represent percentage of respondents for each category.

A. Presymptomatic screening of individuals at risk for *treatable* diseases such as hereditary nonpolyposis colon cancer, which may not manifest until later in life.

B. Presymptomatic screening of individuals at risk for untreatable diseases such as spinocerebellar ataxia type 1 (SCA1), which may not manifest until late in life.

C. General population, presymptomatic screening that identifies individuals at risk for common, treatable diseases such as hypertension.

D. General population, presymptomatic screening that identifies individuals at risk for serious diseases such as breast cancer, though the results are not 100% definitive.

E. Targeted population screening for the identification of carriers of autosomal recessive disorders, such as Tay-Sachs, to determine reproductive options.

F. Population screening for the identification of carriers of autosomal recessive disorders to determine employability or health insurance coverage.

G. Prenatal testing of fetuses at risk for treatable disease which may not manifest until late in life.

H. Prenatal testing of fetuses at risk for untreatable disease which may not manifest until late in life.

I. Prenatal testing of fetuses at risk for being born with a treatable, chronic disease such as Gaucher disease.

J. Prenatal testing for fetuses at risk for being carriers or recessive or X-linked disorders.

bell-shaped distribution as shown in Fig. 1. The mean score was 67%, with no physician responding to all 12 disorders correctly. The second set of questions sought to assess physician understanding of Mendelian genetics (KN2). Six multiple choice questions, related to a genetic testing laboratory report which was provided, tested physicians on their understanding of genetic terms (e.g., heterozygosity and penetrance) and inheritance risks. Responses yielded a bimodal curve as seen in Fig. 2, with a mean score of 64%. The final question set sought to determine physician understanding of the mechanics behind and the proper interpretation of genetic test results (KN3). Two multi-answer, multiple choice questions assessed an understanding of the limitations of genetic testing and of the potential utility of the test results. Partial credit was given for these multi-answer questions. Responses produced a mean score of 65% and a bell-shaped distribution skewed rightward, as seen in Fig. 3. There was no significant correlation between scoring well in KN1 and scoring well in the other two knowledge sets. Physicians who identified themselves as practicing in an "academic" setting did significantly better in sets KN2 and KN3 ($p = 0.002$ and 0.008, respectively) when compared to "private practice" physicians. There was no statistically significant association between those achieving higher scores in the knowledge sets and those physicians who either had recently completed training or taken a formal course in genetics, or who currently read articles regarding genetic testing.

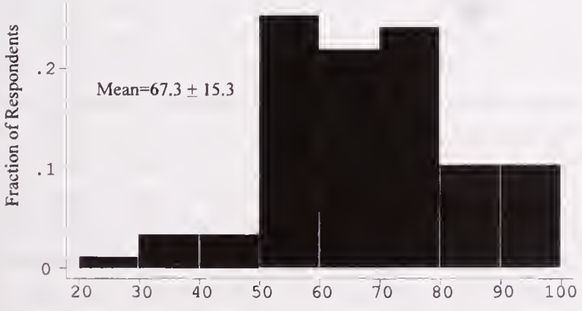

Fig. 1. Genetic test availability correctly identified by physicians for various diseases (KN1).

Counseling

As seen in Table 5, 83 (95%) of 87 respondents believed that the doctor had a responsibility

Table 4
Knowledge of Genetic Test Availability (KN1)
n = 87

Disease	Available	Correct	Incorrect
Alzheimer's Disease	Yes	31 (36)*	56 (64)
Familial Breast Cancer	Yes	67 (77)	20 (23)
Sickle Cell Anemia	Yes	68 (78)	19 (22)
Huntington's Disease	Yes	78 (90)	9 (10)
Fragile-X Retardation	Yes	62 (71)	25 (29)
Diabetes	No	80 (92)	7 (8)
Cystic Fibrosis	Yes	73 (84)	14 (16)
Alcoholism	No	82 (94)	5 (6)
Myotonic Dystrophy	Yes	54 (62)	33 (38)
Hemophilia	Yes	56 (64)	31 (36)
Hypercholesterolemia	Yes	15 (17)	72 (83)
Charcot-Marie Tooth Disease	Yes	38 (44)	49 (56)

* Numbers within parentheses represent percentage of respondents for each category.

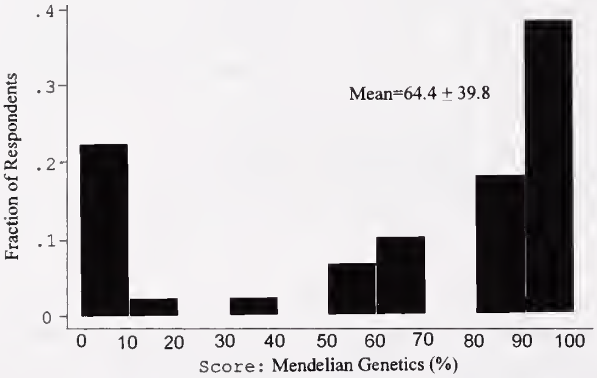

Fig. 2. Correctly answered questions by physicians regarding Mendelian genetics (KN2).

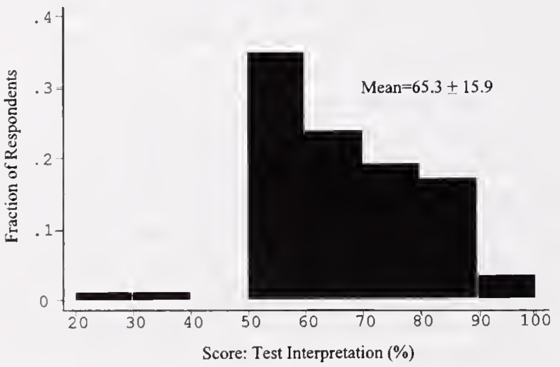

Fig. 3. Correctly answered questions by physicians regarding the mechanics behind and the proper interpretation of genetic test results (KN3).

to provide the patient with counseling. The answer "doctors" was followed by "genetic counselors" (83%), "nurses" (36%), and "social workers" (35%). Only 43 (51%) of 84 respondents, however, believed they actually had the time to discuss genetic counseling issues with their patients. Of 88 respondents, 86 (98%) stated that they would refer a patient for genetic counseling. While 80 (91%) of 88 respondents were aware of genetic counseling services in general, only 62 (71%) of them were aware of such counseling services at the major New York medical centers. And of the 80 physicians who were aware of counseling services, 42 (53%) had referred a patient for these services, with their impressions of the referral found also in Table 5.

Further Information

Of 71 respondents, 48 (68%) were interested in learning more about genetic testing and counseling. Six choices regarding the form in which such information should be offered to physicians (e.g., CD-ROM, audio tapes, seminars) were presented for ranking according to preference. Since no one modality was found to be substantially more preferred than the others, the results of this analysis are not presented in this paper.

Discussion

Our response rate of 26% was below our expectations and below the rates achieved by other study groups that had distributed surveys regarding similar topics (3, 5, 6, 8). Our study, however, unlike most of the other studies reviewed, did not provide incentives (i.e., continuing medical education [CME] credit or financial reimbursement), and our survey was also considerably longer than others. The study of Texas primary care physicians by Friedman et al. (2) had a response rate of 30%, similar to our own rate, without reimbursement. Nevertheless, the number and distribution of our responses were sufficient for analysis.

The majority of our respondents were male and had completed training less than 20 years prior to the study. Furthermore, most respondents identified themselves as specialists. This response reflects the high degree of specialization found at tertiary care hospitals such as Mount Sinai.

Those physicians who had completed training more recently were more likely to have had a formal course in genetics. This was also seen in a study by Hutter et al., in Ontario, Canada (8). Those who identified themselves as currently reading articles regarding testing or as having taken a formal course in genetics rated their

Table 5
Attitudes and Opinions Regarding Counseling

Responsibility to provide the patient with counseling[1]: n = 87			
Doctor	83 (95)*		
Genetic Counselor	72 (83)		
Nurse	31 (36)		
Social Worker	30 (35)		
Receptionist	0 (0)		
Other	5 (6)		
Genetic Counseling	Yes	No	n
Have time to counsel patients:	43 (51)	41 (49)	84
Aware of health professionals known as genetic counselors:	80 (91)	8 (9)	88
Aware of genetic counselors in the New York Area:	62 (71)	25 (29)	87
Would refer a patient to a genetic counselor:	86 (98)	2 (2)	88
Have referred a patient to a genetic counselor:	42 (53)	38 (47)	80
Satisfaction with the referral: n = 41			
Mostly satisfied:	19 (46)		
Very satisfied:	15 (37)		
Neither:	5 (12)		
Mostly dissatisfied:	2 (5)		
Very dissatisfied:	0		

[1] More than one response allowed for the question.

* Numbers in parentheses represent percentage of respondents for each category.

knowledge significantly higher than the other physicians, but did not score significantly higher on the three knowledge sets. The above results could imply that: (1) the issues considered important in our survey are not reflected or addressed in the articles read or courses taken by the surveyed physicians; (2) the courses these physicians took or the articles they read were inadequate for the genetic issues facing physicians today; or (3) since completing their course, the physicians had not kept up with the technological advances in genetics on a regular basis. Primary sources of information for physicians regarding genetics have been shown to include: journals (3, 5, 7, 8), genetics departments (8), colleagues (7, 8), and CME courses and meetings (5, 7). Utilization of most of these sources by Mount Sinai physicians was not assessed in our survey.

The attitudes and opinions expressed about the various scenarios related to genetic testing were fairly consistent with those found in other studies (6, 8). A large majority of physicians in our study failed to support testing for the purpose of employability or health insurance coverage. Other, more controversial issues generated greater division in the responses obtained. Those physicians more likely to counsel patients on such tests themselves are also more likely to be comfortable with ambiguity and confident in their ability to communicate the nature of these tests to their patients (6). Of course, neither controversy nor uncertainty (among physicians or informed lay persons) has stopped numerous clinical laboratories from offering genetic testing to physicians and their patients. So it is only with caution, a solid base of knowledge, and appropriate counseling that a decision as to whether or not to undergo such tests can be properly made.

The low self-rating of knowledge regarding genetics and genetic testing implies that the responding physicians are aware of their limitations regarding the field of genetics. The mean scores for all three knowledge sets were over 60%, similar to findings in other studies assessing physician knowledge (3, 7). Such results, however, must be more closely examined. KN2 had a large standard deviation and produced a bimodal distribution. Physicians scored either very well or very poorly in this section, implying that they had either a satisfactory or an insufficient knowledge of Mendelian genetics. Furthermore, the rightward skew of KN3 implies that although there was a large number of respondents scoring around the mean, there was also a large range of respondent scores on the higher end of the grading scale. The fact that scoring higher in KN1 did not correlate with scoring higher in KN2 or KN3 was also of interest, implying that those physicians who were aware of the availability of various genetic tests were not necessarily able to properly identify those patients at risk and, furthermore, did not necessarily understand the limitations of such tests. Conversely, those physicians who displayed a significantly better understanding of Mendelian inheritance patterns or were aware of the limitations of testing (e.g., those physicians practicing in an "academic" setting) were not necessarily aware of the tests they could be offering their at-risk patients. Either way, patients would *not* be properly informed, either because of a lack of understanding of the tests or because of a lack of awareness of such tests by their physicians. Such a finding was seen in studies regarding colon and breast cancer testing, which showed that patients were referred for testing by their physicians even though the patients failed to meet the recommended criteria and guidelines for the genetic tests (5, 9). The finding that "academic" physicians scored higher than "private practice" physicians in KN2 and KN3 was also true of the survey of almost 1800 physicians by Hofman et al. (7), which showed full-time faculty scoring higher on their knowledge questions than did other non-geneticist physicians. This may be due to the fact that "academic" physicians may have better access to this information through colleagues or nearby departments; however, cannot be determined from the results of this study.

Patient response to genetic test results can be quite varied and can have long-term impact (10–12). With the rapid increase in technology, coupled with the insufficient number of geneticists and genetic counselors, it may be the patient's primary physician who will have to shoulder the responsibility of genetic counseling (13). (Nearly one-third of those responding had already been sent information from a commercial company offering genetic testing.) Furthermore, it is these physicians who will have the duty to help the patient deal with the consequences of the test results, both in terms of offering support and providing preventive measures (4, 13, 14). Genetic testing is ethically difficult because the results affect not only the patient being tested, but the patient's entire family (4, 13). Issues regarding who else can or should be informed about a *potential* predisposition to a disease will be difficult to deal with, especially considering the lack of cures or even agreed-upon treatments for a variety of these diseases (4, 13). While a vast majority of our respondents believed the physician had some responsibility for counseling the patient, only 51% believed they actually had sufficient time. Furthermore, counseling may not be adequate or appropriately nondirective in nature, if given by physicians who are inadequately trained in dealing with these issues (6). While nearly all the respondents would have no difficulty in referring a patient to a genetic counselor, only 71% of them were aware of the services in the New York area. Of those aware of geneticists and genetic counselors, more than half had utilized their services, implying that the demand for such services exists, with most physicians mostly-to-very satisfied with the results.

Of those responding, more than two-thirds expressed interest in learning more about genetic counseling and testing. Unfortunately, no preferred modality for distributing this information was found through our survey, and further research into this is needed.

There are some inherent limitations in our study. The survey was quite lengthy (7 pages) and, due to our own financial and resource limitations, we were not able to offer any incentives to those surveyed. The length, unfortunately, caused many to return only partially completed surveys. While this did not affect most parts of our survey, the final section, in which we inquired about learning more about genetics, was left incomplete more frequently than other sections ($n = 71$ vs. $n > 82$ responding in other sections). Nevertheless, a large majority of those responding to this section did request more information. The low response rate overall, despite its distribution among the various medical fields, may not adequately assess the entire population surveyed. Responses may be biased, as respondents to this lengthy survey may have a stronger interest in genetics, whether due to personal or professional reasons. The small number of respondents also weakened our ability to break down our data further. There were too few physicians to make any significant conclusions about each individual specialty. Though pediatricians are also affected by the new genetic technology, they were not included in this study, as we chose to focus on physicians dealing with adult-oriented diseases.

Conclusions

With genetic technology rapidly changing our understanding of disease and our approach to treatment, it is a challenge for physicians to keep up. There is a need for further education to help physicians become aware of currently available tests, and to help them properly convey the risks and benefits of such tests to their patients. Awareness of the available counseling services needs to be heightened to optimally provide physicians and their patients with the resources and services they desire. Finally, the most effective and efficient methods for providing this information need to be determined.

Acknowledgments

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Replacement of the Pyloric Sphincter with the Ileocecal Valve:

An Experimental Study

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Abstract

Background: Several surgical methods have been devised and applied to overcome the complications associated with the loss of the pyloric sphincter after distal gastrectomy. However, none of these methods creates an efficient sphincteric mechanism at the anastomotic site. The purpose of this experimental study in dogs was to replace the pylorus with the ileocecal valve and determine whether its sphincteric function would be preserved in its new location without affecting gastrointestinal motility and the health of the animals.

Methods: Thirteen dogs underwent surgical removal of the pyloric sphincter and a partial distal gastrectomy. The ileocecal valve, with a short segment of ileum, was then relocated so that the ileal segment was anastomosed to the stomach while the cecal segment was anastomosed to the duodenum. Intestinal continuity was reestablished by anastomosing the distal ileum with the ascending colon. Intraileal and intracolic pressures were measured in all animals prior to and following transposition of the ileocecal valve. In 3 of these animals, pre-pyloric (intragastric) and post-pyloric (intraduodenal) pressures were also measured before the pylorus was removed. Pressure measurements on both sides of the transposed ileocecal valve were performed again 4–6 months later. All pressure measurements were made directly with a water manometer. Radiographic and fluoroscopic studies were carried out on all animals to assess gastrointestinal motility, gastric emptying times, and the sphincteric competence of the transposed ileocecal valve. Hematological and biochemical studies intended to assess the nutritional status of all animals were carried out. Also, postoperative measurements were made of gastric basic acid output.

Results: All animals were alive and well 4–6 months after the initial operative procedure. Hematological studies and biochemical tests and studies of liver function remained normal. There was a slight reduction in serum B_{12} levels and, as expected, a significant postoperative reduction in gastric basic acid output. The intraluminal pressure measurements and the radiographic and fluoroscopic studies all showed that the sphincteric mechanism of the ileocecal valve was preserved in its new location, that gastrointestinal motility was not impaired, and that the healthy condition of the animals was maintained. Gross and histological examination of the transposed segments of the intestinal tract did not reveal any abnormalities.

Conclusion: Because the anatomy and physiology of the human alimentary tract are similar to those of the dog, this technique may be applicable clinically, when indicated, to avoid and/or relieve complications resulting from gastrectomy, when those complications do not respond or have not responded to conservative management. **Key Words:** Pyloric sphincterectomy, ileocecal valve transposition, dumping syndrome, gastrointestinal function.

Introduction

SEVERAL DISEASES of the stomach and duodenum (peptic ulcer and malignant or extensive benign tumors) usually require distal gastrectomy. This approach may involve removal of the pyloric sphincter (1). In such cases, the absence of the pyloric sphincter often results in various complications such as alkaline gastritis, dumping syndrome and anastomotic ulceration (2–6). A variety of surgical methods have been devised to prevent these postoperative complications. However, none of these creates an adequate sphincteric mechanism at the anastomotic site, and none has been proven to be clinically effective in the vast majority of cases (4–8).

The ileocecal valve impedes reflux of the contents of the large intestine and delays the passage of the contents of the ileum toward the large intestine (9, 10). The purpose of this study was to replace the pyloric sphincter in experimental animals (dogs) with the ileocecal valve and to investigate whether the ileocecal valve, in its new position, could serve as a sphincter to delay the passage of gastric content to the small intestine and prevent reflux of the duodenal content toward the stomach. Additional studies were performed to evaluate the overall impact on gastrointestinal motility and general well-being of the animals.

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Materials and Methods

The experiments were performed on dogs because their digestive system is similar to that of humans (11). Thirteen experimental animals, 1 – 2 years of age and weighing 8 – 10 kg were studied. Before surgery, barium X-ray studies of the gastric emptying time and the anatomic condition of the gastrointestinal tract were performed to ascertain the suitability of each animal for the experimental study. Hematological, liver, and biochemical tests (including those for electrolytes and vitamin B_{12} levels), and measurement of nutritional parameters and hourly basic acid output (B.A.O.) were performed preoperatively.

Prior to surgery, the intestine was cleansed and sterilized with neomycin sulfate and metronidazole. Nembutal (16 – 20 mg/kg) was given intravenously for anesthesia. A midline abdominal incision exposed the peritoneal cavity. After isolating the terminal ileum, intraluminal pressures on both sides of the ileocecal valve were performed in order to determine the pressure at which the valve opened. The intraluminal pressures were measured as follows:

1. The terminal ileum was obstructed with a ligature about 8 cm proximal to the ileocecal valve.

2. A Foley catheter was inserted into the ileum through a small opening made distal to this ligature. The balloon was then inflated gently to prevent the catheter from slipping or moving.

3. The Foley catheter was connected to the end of the horizontal segment of a T tube used for measurement of the venous pressure (Fig. 1). The other end of the horizontal segment was connected to a water-filled reservoir (a bottle with colored water). The vertical segment of the T tube was calibrated in centimeters. The zero of the calibrated scale was marked at the level of the eminence of the ileocecal valve. Pressure measurements were carried out as follows: After proper turning of the 3-way valve, the colored water in the water-filled reservoir was allowed to fill the calibrated manometer. Subsequently, by proper turning of the 3-way valve, the water in the manometer was allowed to flow into the lumen of the terminal ileum. When flow ceased for a few seconds, the height of the column of water at that instant was considered to be equal to the pressure required to open the ileocecal valve. When the ileocecal valve opened, flow resumed and the pressure fell to zero. After measurement of these pressures, the Foley catheter was removed, the opening in the ileum was closed, and the ligature was removed.

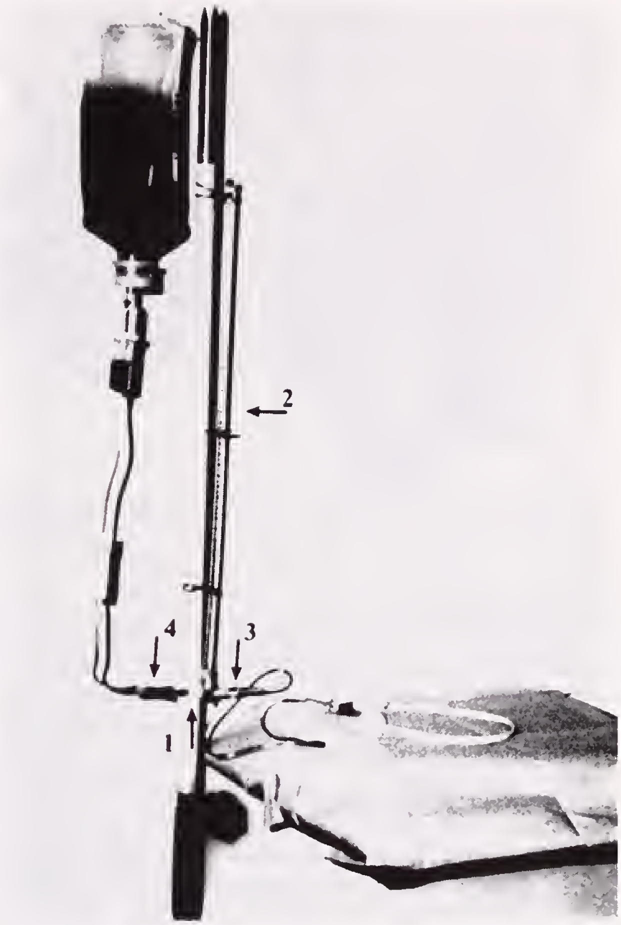

Fig. 1. Apparatus to measure intraluminal pressures. The 3-way valve is marked with arrow 1. The decimal scale in cm is marked with arrow 2. The end of the horizontal segment connected to the Foley catheter is marked with arrow 3. The other end connected to the water-filled reservoir is marked with arrow 4.

Measurement of the intracolic pressure was carried out in a similar manner, except that the Foley catheter was placed in the ascending colon proximal to an occluding ligature positioned about 5 cm distal to the ileocecal valve. The Foley catheter was inserted into the ascending colon through a small incision in the colon, and the procedure described above was repeated.

After all the above measurements had been recorded, a distal gastrectomy with removal of the pylorus and the adjacent segment of the duodenum (1 – 2 cm) was performed. The proximal segment of the ascending colon, with the cecum and a segment (10 – 20 cm) of the terminal ileum, (Fig. 2A) was prepared and isolated. This intesti-

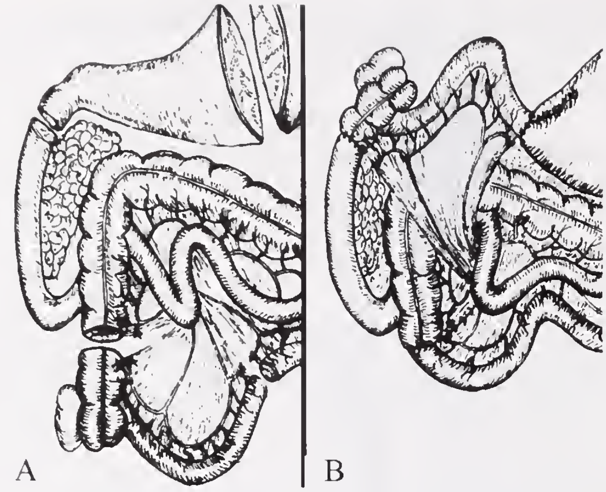

Fig. 2. (A, B) Schematic representation of the surgical technique.

nal segment, with its vasculature and its nerve supply, was then transposed to the site of the excised area of the pylorus. The stump of the transposed portion of the ascending colon was then anastomosed, end to end, with the duodenum. The distal end of the stomach was closed partially and anastomosed, end to end, with the stump of the transposed portion of terminal ileum. The enteric route was then restored by anastomosing the remaining distal end of the ileum, end to end, with the now early portion of the ascending colon (Figs. 2B and 3).

In 3 of the 13 animals, pressures above (intragastric pressure) and below (intraduodenal pressure) the pylorus were measured preoperatively in order to compare these pressures with those after excising the pyloric sphincter. To carry out the intragastric pressures, the stomach was obstructed with a ligature about 5 cm proximal to the pylorus, and a Foley catheter was inserted proximal to this ligature. The intraduodenal pressures were measured by obstruction of the duodenum with a ligature about 5 cm distal to the pylorus, followed by insertion of a Foley catheter proximal to this ligature. The manometer was zeroed at the level of the eminence of the pylorus.

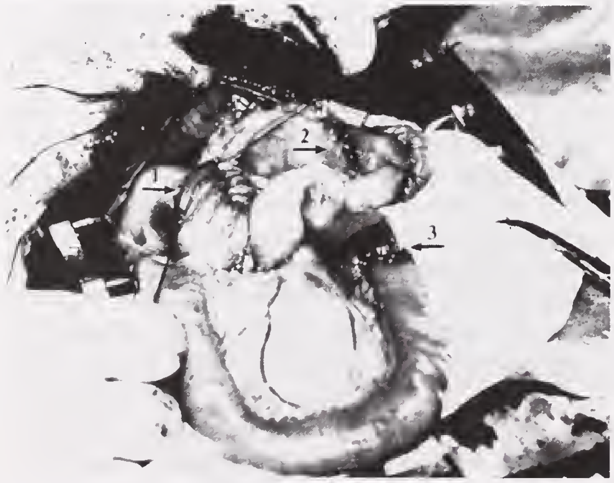

Fig. 3. Final stages of the surgical procedure. The coloduodenal anastomosis is marked with arrow 1; the ileogastric anastomosis is marked with arrow 2; and the ileocolic anastomosis is marked with arrow 3.

To avoid the use of a Levin tube, which is not feasible to place in the dog, a gastrostomy was made and a Foley catheter was inserted into the stomach to overcome the postoperative gastrointestinal paresis. This Foley catheter was also used subsequently to aspirate gastric juice and to infuse barium contrast medium for the X-ray studies of the stomach and gastrointestinal tract. The abdominal wall was finally closed.

During the first few postoperative days, the dogs were hydrated with 5% dextrose solution, administered initially subcutaneously and then by mouth. Prophylactic antibiotics were also given during the early postoperative period. Following this period, a liquid diet was permitted; it was eventually replaced with normal feeding.

Hematological, liver, and biochemical tests, including those of electrolytes and vitamin B_{12} levels, and measurement of nutritional parameters and hourly Basic Acid Output (B.A.O.) of gastric secretion were performed during the postoperative period. Radiographic and fluoroscopic studies of the sphincteric mechanism of the ileocecal valve and of the peristalsis of the stomach, as well as measurements of gastric emptying time, were also carried out during the postoperative period.

After 4–6 months, the animals were re-explored under general anesthesia. Intraluminal pressures, proximal and distal to the transposed ileocecal valve, were carried out to compare these pressures with those obtained preoperatively. The same protocol for pressure measurements was used as described above.

Following measurement of the intraluminal pressures, the animals were sacrificed. The segment of the terminal ileum and ascending colon which had replaced the area of the pyloric sphincter, together with the adjacent segment of the duodenum and stomach, were removed for macroscopic and histological examination.

Results

The experimental animals were kept alive for 4–6 months. During this time, none presented with any illness or weight loss. Nor did the animals experience change in the frequency of bowel movements, which remained at 1 – 2/day, although the stool was looser in the postoperative period. Hematological, liver, and biochemical tests were within normal limits (Tables 1 – 4). The values for B_{12} during the postoperative period were slightly lower (0.06 – 0.07 μg/100 mL) than the preoperative ones (0.08 – 0.09 μg/100 mL) (normal range of B_{12} levels is 0.08 – 0.09 μg/100 mL). The preoperative and postoperative hourly B.A.O. are shown in Table 5. The postoperative values of B.A.O. were significantly lower than the preoperative ones. In the 3 animals studied before the surgical procedure, mean intragastric and mean intraduodenal pressures were 12 and 19 cm H_2O respectively. The preoperative and postoperative intraluminal pressures of the ileocecal valve are shown in Table 6. After transposing the ileocecal valve, the ratio of the intraduodenal/ intracolic and intragastric/intraileal pressures remained unchanged. Moreover, this ratio of intraluminal pressures was similar to that which existed before replacement of the pyloric sphincter in the 3 ani-

TABLE 1

Hematological Tests

Experimental Animal No.	Pre-operative hematocrit %	Post-operative hematocrit %	Pre-operative hemoglobin g/dL	Post-operative hemoglobin g/dL	Pre-operative platelet count x $10^5/\mu$L	Post-operative platelet count x $10^5/\mu$L	Pre-operative white blood count x $10^3/\mu$L	Post-operative white blood count x $10^3/\mu$L
1	41	39	13.2	12.7	6	6	7	10
2	42	40	13.6	12.7	7.5	8	8	12
3	39	37	12.8	12	5	5.5	12	14
4	43	40	14	12.8	4	4	10	10
5	46	43	14.8	14	3.5	4.5	9	9.3
6	41	40	13.2	13	8.5	8	8	8.6
7	40	38	13	12.2	7.3	7.5	7	7
8	39	37	12.8	12	8	7.5	6	6.5
9	47	46	15.2	14.8	7	7	13	11
10	42	39	13.8	12.6	6	6.5	11	9.5
11	40	37	14	12.3	4	3.5	12	12
12	47	44	15.2	14	6	6	15	15.5
13	42	39	13.6	12.8	5	5	16	16

Normal range: hematocrit 37 – 55%; hemoglobin 12 – 18 g/dL; platelet count 2 – 9 X $10^5/\mu$L; white blood count 6 – 17 X $10^3/\mu$L.

TABLE 2

Hematological Tests of Animals

Experimental Animal No.	Pre-operative ALT U/L	Post-operative ALT U/L	Pre-operative AST U/L	Post-operative AST U/L	Pre-operative ALK phosphatase U/L	Post-operative ALK phosphatase U/L	Pre-operative GGT U/L	Post-operative GGT U/L	Pre-operative bilirubin mg/dL	Post-operative bilirubin mg/dL
1	9	14	10	14	20	22	3.4	3.6	0.2	0.4
2	12	17	9	11	16	19	2.6	2.2	0.3	0.5
3	8	10	12	14	17.2	18.5	4.5	4.3	0.2	0.4
4	11	12	9.5	10.3	13	15.5	7.2	5.5	0.3	0.3
5	13	18	11	13	12	12	6.4	3.2	0.1	0.2
6	10	9.5	14	17	19	18.2	3.7	3.5	0.3	0.2
7	8.5	8	13	12	20	20.4	5.2	4.8	0.2	0.2
8	13	12.5	11	10.2	18	15	3.5	3.2	0.3	0.2
9	14	13	12.6	12	21	14	2.8	3	0.2	0.2
10	9.5	9	16.2	15	18	19	4.3	3.8	0.1	0.1
11	10.5	12	18	18	11.5	11	5.6	4.7	0.2	0.1
12	11	11.5	15	14	16.3	14	3.8	3.4	0.1	0.2
13	14	12	12	12.2	15.5	16.5	6.2	5.4	0.3	0.2

Normal range: ALT 8.2 – 57.3 units; AST 8.9 – 48.5 units; Alk phosphatase 10.6 – 100.7 units; GGT 1.0 – 9.7; bilirubin 0.1 – 0.6 mg/dL.

TABLE 3
Biochemical Tests

Experimental Animal No.	Pre-operative calcium mg/dL	Post-operative calcium mg/dL	Pre-operative sodium mEq/L	Post-operative sodium mEq/L	Pre-operative potassium mEq/L	Post-operative potassium mEq/L	Pre-operative glucose mg/dL	Post-operative glucose mg/dL	Pre-operative urea mg/dL	Post-operative urea mg/dL	Pre-operative creatinine mg/dL	Post-operative creatinine mg/dL
1	8.5	9.2	142	138	3.6	3.4	70.2	100.2	12.2	16.8	0.6	0.8
2	8.8	8.5	145	135	4.2	3.7	80.4	90	18.2	19.4	0.7	0.7
3	9.2	10.4	143	140	4.8	4.6	100.2	107	13.8	12.4	0.6	0.7
4	9.3	9.4	146	146	4.2	4.4	90	98	17.2	15.4	0.9	0.7
5	10.5	10.7	152	150.5	5.2	5.5	95	100.3	20.2	16.7	0.6	0.6
6	11.2	11.4	146	145.7	3.8	3.8	97.4	100.6	18.6	14.5	0.9	0.8
7	8.7	9.2	140.8	140.2	4.2	4.4	88	90.2	11.8	9.5	0.7	0.6
8	9.6	9.7	149	150.8	4.6	4.8	90.4	100	14.8	12.5	0.8	0.7
9	10.3	10.5	150.2	152	5.2	5	90.6	102	17.2	14.8	1.2	0.9
10	10.6	10.3	144.8	150	4.5	4.8	90.3	107	16.5	11.8	0.9	0.8
11	11.4	11.4	138	145	3.9	4.1	100.7	111	22.6	17.3	1.2	0.8
12	11.2	11	140	142.8	4.3	4.7	100.2	108	20.8	18.3	1.4	0.9
13	9.6	10.2	139	141.8	5.2	5.5	98	106	17.6	12.8	1.2	0.8

Normal values: calcium 8.7 – 11.8 mg/dL; sodium 140.3 – 153.9 mEq/L; potassium 3.8 – 5.6 mEq/L; glucose 61.9 – 108.3 mg/dL; urea 8.8 – 25.9 mg/dL; creatine 0.5 – 1.6 mg/dL.

TABLE 4
Nutritional Parameters

Experimental Animals No.	Pre-operative	Post-operative	Pre-operative	Post-operative
	Albumin g/dL		Protein G/dL	
1	2.7	3.2	4.2	4.8
2	2.5	3.7	5.3	6.2
3	2.8	4.2	5.6	7.2
4	3.0	3.8	5.8	7.0
5	3.2	4.2	6.2	7.4
6	2.8	3.8	5.5	7.3
7	2.5	3.7	5.3	6.8
8	2.6	3.6	5.6	7.1
9	3.2	4.5	5.8	7.8
10	2.5	3.7	5.5	7.2
11	2.4	3.5	5.2	6.8
12	2.8	4.2	5.7	7.8
13	3.3	3.8	6.2	7.4

Normal values: albumin 2.6 – 4.0 g/dL; total protein 5.5 – 7.5 units.

mals in which these measurements were carried out. For this reason, no reflux of duodenal contents was observed fluoroscopically in any animal. The radiographic (Fig. 4) and fluoroscopic studies showed preservation of both the sphincteric mechanism of the ileocecal valve in its new position and of the peristalsis of the stomach. Preoperative and postoperative gastric emptying times, measured until the stomach was virtually free of barium, were similar in all animals (Table 7) (13). No abnormal findings were noted in either the macroscopic (Fig. 5) or histological examinations.

Discussion

The results of the present study demonstrate that when the pyloric sphincter of the dog is replaced with the ileocecal valve, the sphincteric mechanism of the ileocecal valve is preserved in its new position. This serves to prevent rapid gastric emptying as well as duodenal reflux. Moreover, Dozois and Kelly have reported that gastric emptying time of dogs with distal antrectomy did not differ significantly from that of control animals (14).

The consequences of removing the ileocecal valve from its normal location (impairment of

TABLE 5
B.A.O. Measurements

Experimental Animal No.	Hourly pre-operative B.A.O. * mEq/L	Hourly post-operative B.A.O. ** mEq/L
1	6.7	4.5
2	6.5	3.8
3	6.4	3.0
4	6.4	2.8
5	6.5	3.2
6	6.6	4.0
7	6.5	3.4
8	6.6	3.5
9	6.7	4.2
10	6.6	4.0
11	6.5	3.8
12	6.6	4.6
13	6.4	3.8

Normal range: 6.4–6.8 mEq/L.
* Mean ± S.D. = 6.07 ± 0.1; ** 3.73 ± 0.54; $p < 0.001$ (paired t-test)

the absorptive function of the small intestine and loose stool), can be managed effectively with medical treatment (12), in contrast to the clinical difficulties which often arise following gastrectomy.

Vitamin B_{12} deficiency is expected in the long term, and this should be considered as one disadvantage of the procedure. However, B_{12} deficiency can easily be corrected with periodic B_{12} injections. Reduced B.A.O. follows distal gastrectomy, but this could be helpful in preventing ulceration at the anastomotic site.

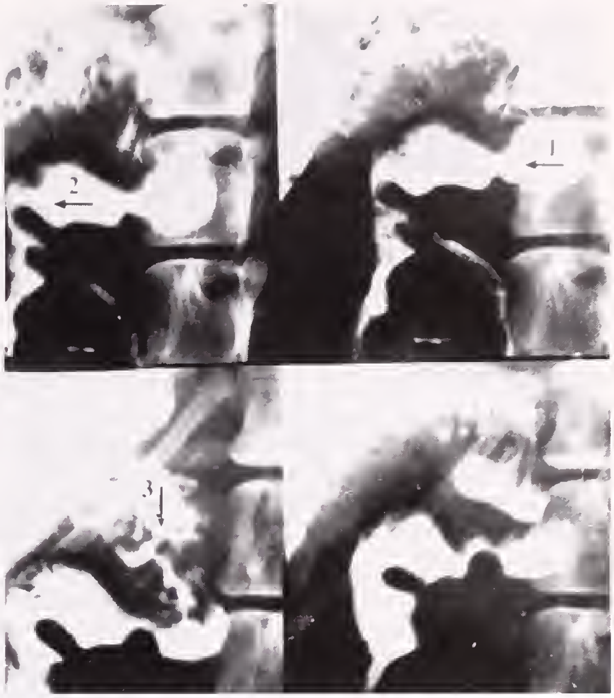

Fig. 4. Radiologic depiction of ileocecal valve function in one of the experimental animals. The fluctuations in the opening of the ileocecal valve confirm preservation of its sphincteric mechanism. Preservation of peristalsis of the stomach is also shown. The ileocecal valve is marked with arrow 1; the coloduodenal anastomosis is marked with arrow 2; and the ileogastric anastomosis is marked with arrow 3.

Conclusion

The healthy condition of the dogs after the procedure, the normal blood and serum laboratory

TABLE 6
Intraoperative Intraluminal Parameters *

Experimental Animal No.	Pre-transposition Pressures cm		Post-transposition Pressures cm	
	Intrailiac	Intracolic	Intragastric	Intraduodenal
1	14	31	12	28
2	25	38	20	35
3	16	30	15	32
4	20	40	18	37
5	13	27	10	25
6	20	36	17	34
7	14	32	14	30
8	15	31	13	28
9	14	34	15	33
10	13	28	10	23
11	14	29	12	26
12	16	30	15	30
13	21	40	18	38
Mean ± S.D.	16 ± 3.8	32.8 ± 4.4	14.5 ± 3.1	30.7 ± 4.6

* In 3 animals, mean *in situ* intragastric and intraduodenal pressures prior to the surgical transposition of the ileocecal valve were 12 and 19 cm respectively.

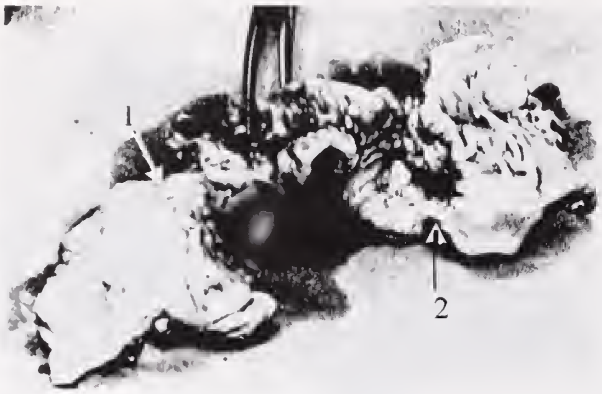

Fig. 5. Macroscopic presentation of the area of the ileocecal valve with the adjacent duodenal and gastric segments in one of the experimental animals. The coloduodenal anastomosis is marked with arrow 1 and the ileogastric anastomosis is marked with arrow 2. The clamp shows the position of the cecum.

TABLE 7
Gastric Emptying Time

Experimental Animal No.	Preoperative min	Postoperative min
1	60	60
2	80	70
3	70	65
4	80	75
5	45	45
6	70	70
7	50	50
8	60	60
9	45	40
10	40	40
11	50	45
12	80	80
13	90	90

Normal range: 30–60 minutes (13).

values, the radiographic and fluoroscopic studies, and the macroscopic and histological examinations all showed that this technique is feasible and effective in the animals studied. Because the anatomy and physiology of the alimentary tract in the dog is similar to that of humans, this method might provide better clinical outcomes following gastrectomy than those achieved with the present-day techniques. This method might also be useful in relieving postgastrectomy complications which do not repond or have not responded to conservative treatment.

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Gallstone Ileus and Crohn's Disease without Biliary-Enteric Fistula:

Report of a Unique Case

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Abstract

Gallstone ileus is an uncommon cause of small bowel obstruction, accounting for fewer than 3% of laparotomies for intestinal obstruction. Patients with long-standing Crohn's disease have an increased risk of developing gallstone disease. However, gallstone ileus is not common in these patients. We report the case of a 70-year-old female with Crohn's disease who presented with gallstone ileus, and present a review of the literature. We discuss the association between gallstone ileus and Crohn's disease, and the treatment options for these patients. We emphasize the importance of including gallstone ileus in the differential diagnosis in patients presenting with intestinal obstruction, especially patients with long-standing Crohn's disease. We advocate the early utilization of computerized tomography to confirm the diagnosis, and prompt early surgical intervention. **Key Words:** Crohn's disease, gallstone ileus.

Introduction

GALLSTONE ILEUS is an uncommon cause of small bowel obstruction. It accounts for fewer than 3% of laparotomies for intestinal obstruction. Most patients are over the age of 65 and female (1). A cholecystoduodenal fistula is found in the majority of cases. The stone is typically of large size and the usual site of impaction is the distal ileum (2). Treatment is laparotomy and relief of obstruction by enterolithotomy. Patients undergoing surgery for gallstone ileus have reported mortality and morbidity rates of 11.7% and 32%, respectively (1).

Patients with long-standing Crohn's disease have an increased risk of gallbladder disease (3), but there are few reports of gallstone ileus in these patients. The increased risk of gallbladder disease is attributed to the disturbance in the enterohepatic circulation of bile salts secondary to disease of the terminal ileum and a resultant change in cholesterol solubility leading to the increased formation of gallstones (4).

We report a case of a 70-year-old female with Crohn's disease who presented with gallstone ileus requiring surgical intervention, and present a review of the literature. We discuss the association between gallstone ileus and Crohn's disease, and the treatment options for these patients.

Case

A 70-year-old female with a 35-year history of Crohn's disease involving the terminal ileum was admitted for small bowel obstruction. Her past medical history was significant for breast cancer requiring left mastectomy at the age of 49, and mild chronic bronchitis. Medications were beclomethasone inhalers and diphenoxylate. The diagnosis of Crohn's disease was first made at the age of 35, at exploratory laparotomy in which the diseased terminal ileum was left *in situ* and an ileotransverse colon side-to-side anastomosis was performed. At the age of 42, the patient had resection of the bypassed segment for intractable

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Crohn's disease, and the previous ileocolic anastomosis was left intact. After the second operation, the patient remained relatively asymptomatic and complained only of occasional episodes of intermittent abdominal pain. On the day of admission, the patient developed increasing abdominal pain and distention, nausea and bilious vomiting. On physical examination, the abdomen was distended and tympanitic without signs of peritonitis. An obstructive series was consistent with small bowel obstruction and an opacified density in the left abdomen was noted (Fig. 1). Computerized tomographic scan (CT scan) of the abdomen showed this opacified mass to be intraluminal and highly suspicious for a gallstone (Fig. 2). Sonogram of the abdomen revealed sludge in the gallbladder, without biliary dilatation. The patient was rehydrated and taken to the operating room 24 hours after admission. Exploratory laparotomy revealed distended loops of small bowel and a clear transition zone from dilated to collapsed bowel just proximal to the previous ileotransverse colon anastomosis. A 3.5 cm stone was palpated at this site. The neoterminal ileum was diseased and strictured secondary to Crohn's disease. The neoterminal ileum, along with adjacent colon, was resected and a primary anastomosis was performed (Fig. 3). Adhesions to the gallbladder were taken down, and the gallbladder was visualized and palpated. There were no signs of inflammation, there were no palpable stones, and there was no fistulous communication between the gastrointestinal tract and the gallbladder. No other stones could be palpated in the duodenum, small bowel or large bowel. The patient's postoperative course was uneventful and she was discharged on the ninth postoperative day. Polarized microscopic analysis of the stone (LabCorp, Burlington, NC) showed that calcium bilirubinate was the main component, comprising 80% of the

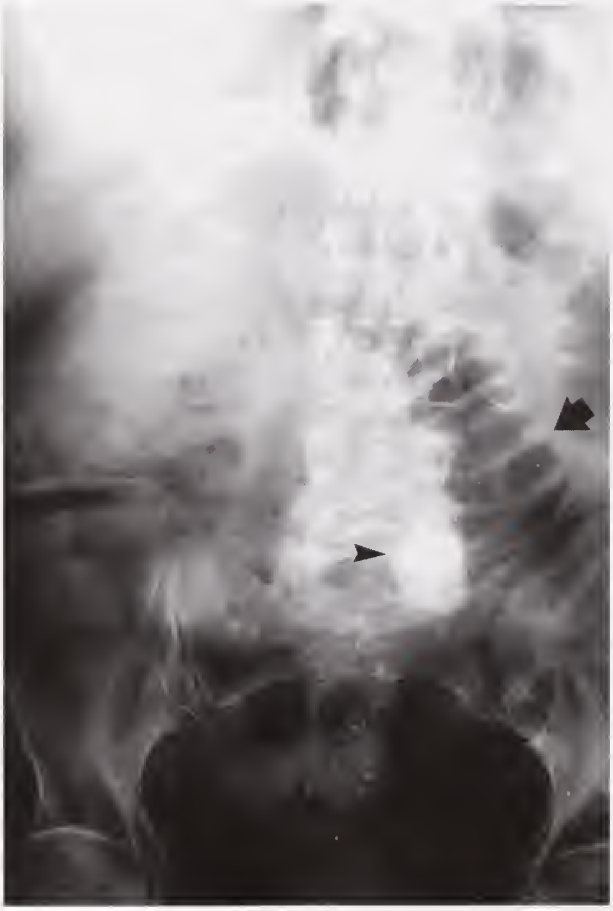

Fig. 1. Plain abdominal radiograph showing dilated loops of small bowel (arrow) and a calcified mass in the left abdomen (arrowhead).

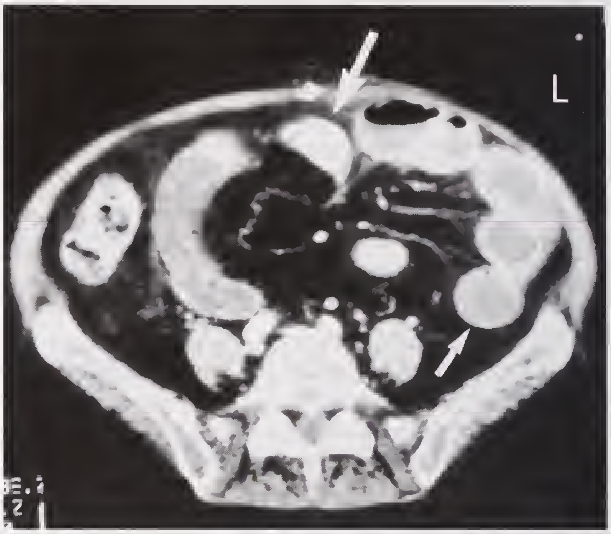

Fig. 2. Computerized tomographic scan of the abdomen demonstrating dilated loops of small bowel (small arrow) and an intra-luminal calcified mass (large arrow). The intrahepatic and extrahepatic bile ducts were normal.

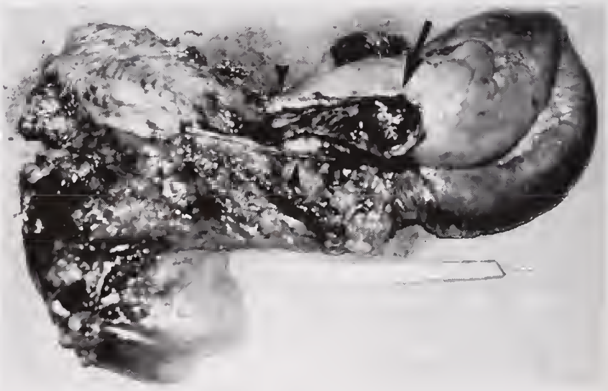

Fig. 3. Photograph of the surgical specimen showing the stone (arrow) impacted in a segment of diseased and strictured small bowel (arrowheads).

stone and all of the core. Gross and microscopic examination of the distal ileum confirmed Crohn's disease.

Discussion

Gallstone ileus accounts for fewer than 3% of laparotomies for small bowel obstruction (2). Most patients are over the age of 65 with a male to female ratio of 1:5 to 1:10. Biliary symptoms are common, but the diagnosis is made preoperatively in less than 50% of cases (5). The most common pathology is a cholecystoduodenal fistula, although fistulous connections have been reported to the jejunum, colon and stomach (6). A few case reports of intestinal obstruction caused by stones without a fistulous communication have been reported. As was previously suggested, a possible explanation can be the migration of a small stone through the papilla of Vater and "*in-situ* growth" in strictured small bowel (7).

Because its luminal diameter is small, the ileum is the most frequent site of impaction, but stones have been found impacted from the stomach to the sigmoid colon (8). Symptoms are usually intermittent and consistent with partial intestinal obstruction, the so-called "tumbling phenomenon." A flat plate of the abdomen will reveal small bowel obstruction, air in the intrahepatic ducts, and a mobile opacified mass in 25% of patients (9). In the present case, abdominal radiographs were consistent with small bowel obstruction and a calcified mass was found, but air in the intrahepatic ducts was not noted. Treatment is laparotomy with relief of the obstruction. Cholecystectomy and repair of the fistula, when present, are subjects of controversy.

Crohn's disease is strongly associated with gallstone disease. The prevalence is especially high in patients with Crohn's disease of the terminal ileum and in patients after ileal resection (3, 10). Cholesterol is the main component of most cases of gallstones in patients with Crohn's disease. The pathogenesis is attributed to the disturbance in the enterohepatic circulation caused by decreased absorption of bile salts, secondary to Crohn's disease, or because of resection of the terminal ileum. The diminished pool of bile salts changes the solubility of cholesterol in bile, causing cholesterol to precipitate (4). Ileal dysmotility has also been suggested as a cause. Lapidus, however, found that the concentration of bilirubin in bile in patients with Crohn's disease after ileal resection is 45–50% higher than in healthy controls (11) and suggested that patients with Crohn's disease develop pigment stones rather than cholesterol gallstones. Increased concentration of bilirubin in a segment of the small bowel may enhance "*in-situ* growth" of a small pigment stone. This can be a possible explanation for the finding of a stone comprised mainly of calcium bilirubinate in a patient without a fistulous communication to the gallbladder, as was the case in this patient.

An association between Crohn's disease and gallstone ileus is rare (12, 13); only three cases have been reported. The mean age was 60.3 years (50–67 years), with a mean duration of disease of 13.7 years (4–20 years). Mean stone size was 2.5 cm (1.5–3 cm), considerably smaller than reported for patients without Crohn's disease (mean 4.5 cm, range 2–9 cm). This is presumably due to the already narrowed small bowel lumen secondary to the fibrostenotic Crohn's disease. Accordingly, the patient we present belongs to an older group of patients, with long duration of disease, who presented with intestinal obstruction caused by a small stone.

Of the three known cases in the literature of Crohn's disease complicated by gallstone ileus, only one had biliary symptoms. The diagnosis of gallbladder disease in patients with Crohn's disease can be missed as a result of the predominance of intestinal symptoms in these patients. In a review of 1001 patients with gallstone ileus, preoperative diagnosis was made in only 43% (1). Only one of the three patients with gallstone ileus and Crohn's disease was diagnosed preoperatively. In patients with Crohn's disease presenting with uncomplicated small bowel obstruction, medical therapy is generally the first line of treatment, because much of the luminal narrowing may be related to inflammation which may be treated pharmacologically. Also, unlike adhesive obstruction, ischemia and gangrene of the bowel is very rare in this group of patients. As was previously reported, the addition of a CT scan in this case to confirm the diagnosis prompted early surgical intervention (14).

Laparotomy revealed the stone to be impacted in a strictured segment of diseased small bowel. In patients with Crohn's disease, obstruction at a strictured and diseased segment of bowel, even with a small stone, is not surprising. Furthermore, with the combination of lithogenic bile and small bowel narrowing due to Crohn's disease, a higher incidence of gallstone ileus in patients with Crohn's disease might be expected.

The operative approach to gallstone ileus is enterotomy, extraction of the stone and a careful search for more stones and a biliary-enteric fistula (1). We were faced with a more complex problem due to the fact that the stone was impacted in diseased bowel. The approach in such a patient should be different and include a procedure that resects, bypasses, or widens the strictured segment of small bowel. Our patient, as well as the three previously reported cases, underwent ileocolic resection and restoration of bowel continuity.

Conclusion

We present a case of a 70-year-old female with long-standing Crohn's disease who presented with intestinal obstruction secondary to gallstone ileus. Early surgical intervention was prompted by the use of CT scan to confirm this uncommon diagnosis. Intestinal obstruction was caused by a small gallstone impacted in strictured ileum secondary to Crohn's disease. No bilio-enteric fistula was found. The differential diagnosis of intestinal obstruction should always include gallstone ileus, especially for patients with long-standing Crohn's disease. The operative approach is resection of the segment of bowel with restoration of bowel continuity. A search for a fistulous communication between the biliary tract and the intestine is also necessary.

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An Integrated Program for Evidence-Based Medicine in Medical School

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Abstract

To provide optimal care for their patients, clinicians must be able to locate and interpret the most current literature. Teaching the necessary skills to medical students is essential, if we wish to train clinicians to be able to keep up with the expansion of biomedical knowledge for their entire working lives. In this paper, we describe our school's four-year curriculum in evidence-based medicine and the performance of three senior classes on the summative evaluation exercise devised to measure the program's success. **Key Words:** Evidence-based medicine, curriculum, library skills.

Introduction

The rapid expansion of biomedical knowledge makes it difficult to keep up with new developments. While physicians have always needed the skills to acquire and evaluate current information, the volume of information, with its variable quality and clinical relevance, has created a formidable challenge. Evidence-based medicine (EBM), which consists of formulating clinical questions, retrieving and evaluating the evidence from the literature, and applying the obtained information to the clinical problem at hand, has gained wide acceptance as an important strategy to meet these challenges (1, 2).

We have incorporated the teaching of EBM into our four-year curriculum as part of our overall goal of training medical students to be lifelong learners, the importance of which was underscored in the 1984 GPEP Report (3). We are unaware of any published examples of comprehensive four-year medical school programs in EBM. In this paper, we describe the program introduced in 1996, and report the performance by senior students on the summative evaluation developed to assess the program's success.

Methods

The initial step in introducing EBM into all four years of our medical school curriculum was the creation, in the fall of 1995, of an Evidence-Based Medicine Working Group. It consisted of faculty from the Dean's Office, the Library, and the departments of Medical Education, Medicine, Pediatrics, Surgery, Geriatrics, Health Policy, and Community Medicine. Members met with all preclinical course and clinical clerkship directors to determine the extent to which EBM was taught in our traditional curriculum, and to explore new strategies for instruction and evaluation. The four-year curriculum (Table 1) was introduced in

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TABLE 1

Evidence-Based Medicine Program Components

Courses	EBM Component
Library Sciences	2-hour small-group session on MEDLINE, demonstrating basic search strategies, as part of 7.5 hour course; advanced instruction integrated into the Epidemiology/Biostatistics curriculum.
Epidemiology	Students must critique articles offered as evidence in the environmental medicine module.
Microbiology	Use of the literature is required to identify unknown laboratory specimens.
Clerkships	All students attend library module on question/search formulation in first rotation of the third year.
Medicine	Each student presents the answer to a clinical question based on one of their own patients, with a critique of the evidence (3 – 4 students/group preceptor session); Prognosis module.
Pediatrics	Each student presents the answer to a clinical question based on one of their own patients, with a critique of the evidence (3 – 4 students/group preceptor session); Overview module.
Psychiatry	Each student presents the answer to a clinical question based on one of their own patients, with a critique of the evidence (3 – 4 students/group preceptor session); Therapy module.
Surgery	Course director and library staff present sessions on basic EBM topics; Harm module.
Ob/Gyn	Three oral presentations require use of primary sources. Students attend a housestaff journal club and 3 one-hour student journal clubs; Diagnostic Test module.
Neurology	Students perform searches based on patient encounters.
Community Medicine	Students present an in-depth critique of one article used in a research paper; MEDLINE review by Library staff in preparation for research project; small-group EBM session.
Geriatrics	Small group preceptor prepares a clinical question; students give a 15-minute oral presentation of search findings, including a critique of one article.

academic year 1996 – 1997; the Class of 2000 is the first to be exposed to this program in its entirety. Faculty development occurred on a number of different levels, including a full-day retreat at which four faculty members from McMaster University trained twenty-four course and clerkship directors to teach EBM. These individuals acted as trainers for the remainder of the faculty in their departments.

The preclinical years introduce the students to medical informatics and the skills needed to appraise the literature, and allow them to practice their presentation skills. The Library Science and Medical Informatics Course, presented in the first month of the first year, was expanded from 4 to 7$^1/_2$ hours to allow for more comprehensive small-group, hands-on discussions of information resources and services, the use of the MEDLINE database, computer-assisted instruction, and Internet applications. Librarians teach advanced on-line search strategies for evidence-based medicine prior to the Epidemiology course, which teaches critical appraisal skills in its environmental medicine module (4). In 1998, the Library staff began assisting in the Microbiology course, providing small-group, hands-on instruction in MEDLINE searching and assisting students in finding articles needed to identify unknown laboratory specimens.

The curriculum for the clinical years is based on the principles developed at McMaster University and published in the "Users' Guides to the Medical Literature" (5 – 14). Their group has developed a model that teaches medical students how to ask a clinical question based on an individual patient, search for articles in a database, appraise the articles retrieved, and apply the information to the patient's problem, for a variety of issues (therapy, harm, diagnostic tests, etc.). A one-hour session during orientation to the third year is used to define the goals and objectives of the curriculum and to describe the components in each rotation. Since the students in the classes of 1998 and 1999 were not exposed to the expanded Library Science curriculum during their first two years, library staff provided those students instruction on MEDLINE use during the Surgery and Pediatrics third-year clerkships.

The curriculum in the third year uses a two-pronged approach. Each department teaches one of the McMaster modules, and students must demonstrate proficiency in the application of evidence-based medicine to patient care. In Pediatrics, students are taught the methodology for appraising an overview article, in a large group lecture. The preceptors help each student define a clinical question related to a case presentation. Students are required to do a literature search and present the findings, including a critique of the evidence, at a small group session later in the rotation. In Medicine, students are given an article on the prognosis of untreated hypercholesterolemia, a handout explaining the appraisal methodology for this type of article, and a worksheet. Preceptors review student critiques one week later, in a small-group session, and also evaluate their ability to apply EBM in an exercise identical to the one described above. In Psychiatry, a small-group session is devoted to the analysis of an article on the therapy of obsessive-compulsive disorder; EBM is applied clinically as it is in Pediatrics and Medicine. The harm module is taught in the Surgery clerkship. Students generate a clinical question, identify pertinent articles from MEDLINE, and critique the evidence, using the McMaster methodology. The methodology needed to evaluate an article on diagnostic tests in taught by lecture in Obstetrics/Gynecology, and students use the literature to prepare presentations for rounds, small groups, and journal club. Students use the literature to prepare for case-based presentations in Neurology.

Small-group sessions on evidence-based medicine have been added to the curriculum of the fourth-year Community and Preventive Medicine course, and students must now provide a formal critique of one of the articles used to prepare their required preventive medicine papers. The library staff provides an additional two hours of instruction in MEDLINE use during this course. In the fourth-year Geriatrics clerkship, a question prepared by the course director is the basis of a small-group discussion.

Evaluation Strategies

In collaboration with the clerkship directors, the Working Group developed strategies to analyze students' exposure to medical informatics both prior to and during medical school, and to assess the success of the new curriculum. A questionnaire was developed to assess incoming and senior students' computer literacy and the extent of exposure to formal instruction. Student performance in each of the EBM exercises described earlier is evaluated, and the result contributes to the overall grade for the course or clerkship.

We created an exercise designed to quantify fourth-year students' skills in information retrieval and critical reasoning. In order to allow standardization of the exercise, clinical questions, with known answers that could be searched using EBM strategies, were designed. The Working Group developed four clinical questions (Table 2), identified relevant articles with good study design, and determined appropriate answers to each question. These questions were based on cases in the fourth-year Clinical Competency Examination, a mandatory standardized patient exercise that assesses students' communication, history taking, physical examination and clinical reasoning skills. Each student was randomly assigned one question and given four weeks to submit a printout of their literature search strategy and five relevant citations, along with a one paragraph answer to the question which must include a critique of the single most relevant article.

Staff librarians use a five-point scale (not demonstrated/limited/good/very good/excellent) to rate the efficiency and accuracy of students' search strategies. A five-point scale (not demonstrated/poor/adequate/very good/complete) is also used to rate how well the student addressed three core issues: validity (whether the relevant methodological questions were addressed), results (the findings of the study), and relevance (whether the study applied to the question at hand).

The class of 1997 served as a baseline group because they had completed their first three years of medical school prior to the introduction of formal EBM instruction. Participation was optional for this class, and only 56 of the 120 students in

TABLE 2
Evidence-Based Medicine Exercise Questions

1. JR is a two-year-old child with asthma. You have recommended treatment with beta- adrenergic agonists, but the mother is concerned that these drugs may have an adverse effect on her child's health. Conduct a MEDLINE search to determine if there is any evidence which refutes or supports her concerns.

2. KB is a forty-one-year-old woman with acute right upper quadrant pain. As the surgical consultant, you need to determine if she has a gallbladder disorder. Using the most recent MEDLINE segment, formulate and run an effective search to determine the best way to diagnose gallbladder disease in this patient.

3. MH, a patient with sickle cell anemia, presents in painful crisis to the Emergency Room (ER). He has been in the ER six times in the past two months, and received oxygen and IM Demerol. You need to determine an alternative pain management regimen that will keep him out of the ER and shorten the duration of his crisis. Use MEDLINE to identify literature on this topic, and formulate a treatment plan.

4. JT is a fifty-one-year-old patient with Type II diabetes mellitus. He has concerns about the likelihood that he will have loss of vision or a heart attack. Conduct a MEDLINE search to help you answer his concerns about developing either of these complications.

the class (47%) participated; subsequent classes have been required to perform the exercise.

Results

Medical Informatics questionnaires: Beginning with the class of 2000, incoming students have filled out a medical informatics questionnaire. The classes of 2000, 2001, and 2002 have reported extensive experience with computers, e-mail, and literature searches. However, more than 60% of the students received no formal instruction in the skills required for evidence-based medicine.

At graduation, more than 97% of the senior students in the classes of 1997 and 1998 reported extensive experience with literature searching. Not surprisingly, only 3% of the class of 1997, which served as the baseline year, reported formal instruction in evidence-based medicine skills.

Fourth-Year EBM Exercise: The fourth-year exercise has been given to the classes of 1997, 1998, and 1999; data were analyzed using chi-square. Fig. 1 presents the results of the library skills' evaluation. Overall, there has been a slow but steady improvement in search skill strategies used to locate articles needed to answer the clinical question. We have seen statistically significant improvement in student use of keywords to identify main concepts, appropriate MeSH headings (Medical Subject Headings), subheadings, combined multiple headings, and limiting search strategies by publication type and to English-language journals.

Fig. 2 presents the data for the classes of 1997, 1998 and 1999 on the use of EBM methodology. Over the course of the years, the students have shown increasing ability to address issues of validity and results. The class of 1998 addressed the relevance of the articles better than did the baseline class; this improvement was not sustained for the class of 1999.

As demonstrated in Table 3, more than 95% of students in the three cohorts submitted the full-text articles used as the basis for their answer. There was improvement over the three years in the percentage of students performing a critique, but there was not a significant improvement in the number of students who reached the correct conclusion. The percentage of students in the class of 1999 who omitted relevant articles tended to be smaller.

TABLE 3
EBM Exercise Evaluation

%	1997 n = 56	1998 n = 100	1999 n = 100
full-text article submitted	95	97	97
correct answer	66	87	75
critique done	71	75	91
relevant articles omitted	69	79	57

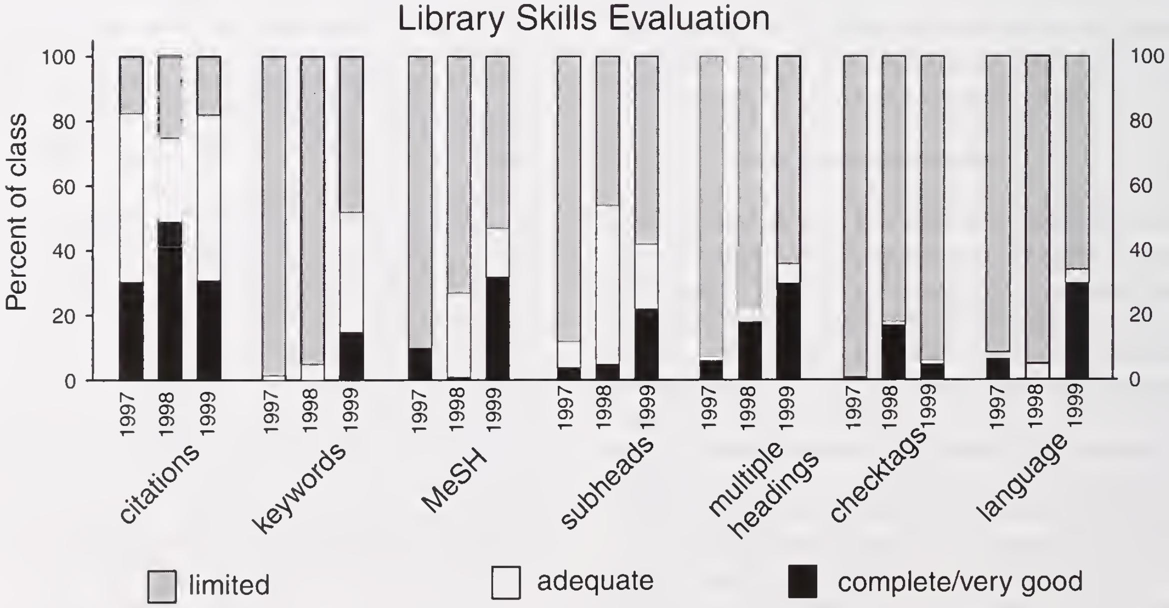

Fig. 1. Library Skills Evaluation. The graph shows data from the classes of 1997 through 1999. The n's are as shown in Table 3. The five-point scale described in the body of the paper was collapsed by grouping under the heading of "limited" those students who did not demonstrate usage of the MEDLINE filters with those who showed limited ability. There appears to be a trend toward improvement in the use of keywords, MeSH, subheadings, combined multiple headings and limiting to English language journals. There is not much difference in the ability to identify relevant citations or in the use of checktags.

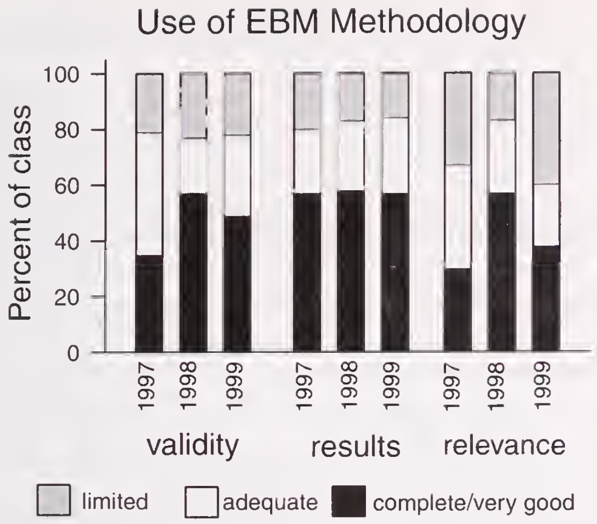

Fig. 2. Use of EBM methodology. The numerical symbols and definitions are as described in Fig. 1. There appears to be a trend toward enhanced ability to identify the validity (whether the relevant methodologic questions have been addressed) and results of studies.

Discussion

We have developed a four-year, integrated EBM curriculum that uses the basic science courses to teach basic EBM skills and the clinical clerkships to teach a more sophisticated approach. The ability to use EBM in patient care is one of the factors used by the preceptors when they grade the students. Finally, an outcome measure was developed to gauge the success of our program and to identify weaknesses to be addressed in the future.

To our knowledge, this is the first attempt at a four-year, integrated EBM curriculum. There are a few reports that describe the integration of EBM skills into selected components the preclinical years (15–19). Other reports describe the teaching of information retrieval skills as part of the curricula for the clinical years (20–25). Furthermore, a four-year curriculum limited to teaching information retrieval skills has been described (26, 27), as have instructional programs limited to critical appraisals (28–33).

It is also apparent that EBM cannot be taught dependably in residency training programs. Residents currently in training do not have these skills (34), there are few published curricula for housestaff (34, 35), and residents exposed to critical appraisal curricula have not shown significant improvement in their skills (33).

Our ability to create an EBM curriculum resulted from two factors. Most important, both basic science and clinical faculty cooperated to develop and implement a comprehensive EBM curriculum. Second, the faculty development that preceded implementation was an important foundation. There is, however, much work that remains to be done. Although students seemed to have performed better on our assessment measures, we believe that more data in subsequent years will be required before any definite conclusions can be made regarding the effectiveness of our current approach. We believe that students must identify the relevance of articles and improve their ability to reach the appropriate conclusions. Furthermore, the reliability and validity of the fourth-year assessment tool that we created has not been formally assessed. Like many schools, we are in the process of implementing a new curriculum, which will include a longitudinal clinical component from the first day. Incorporating the teaching of EBM into all components of the new curriculum, increasing the use of literature articles instead of textbooks as primary sources, and nurturing and rewarding teachers who use EBM in an innovative manner are challenges we are eager to meet.

In conclusion, using data from the EBM exercise, we will continue to refine and expand our program in evidence-based medicine. We believe that through this curriculum, we will be able to train students who will be more effective residents and, ultimately, practicing physicians, best able to handle the explosive growth of biomedical knowledge.

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Letter to the Editor

Clinical Trials in Hypertension:

An Uncertain Impact on Physician Practice

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Dear Sir:

Research in hypertension continues to explain more about the pathogenesis of this condition and the underlying changes in vascular biology that can lead to cardiovascular events. But despite this exciting work, two ongoing issues continue to be highly relevant: first, that effective control of high pressure should remain the cornerstone of management; and second, that many clinicians still are not sufficiently focused on adequately achieving treatment goals. The purpose of this letter is to draw attention to some recent developments in these areas.

Clinical trials in hypertension during the last 30 years have provided consistent evidence that blood-pressure-lowering treatment reduces the number of major clinical events and improves survival in hypertensive patients. This experience has included hypertension of differing degrees of severity, and has shown the benefit of treatment in systolic as well as diastolic hypertension, and in the elderly as well as in the younger patient (1, 2). Newer trials have shown that aggressively treating blood pressure to reach relatively low target goals — systolic blood pressures in the low 130s and diastolic blood pressure in the low 80s — appears to provide even greater protection against serious endpoints than when blood pressure is reduced to the more traditional goal of 140/90 mm Hg (3). Patients at heightened risk of poor outcomes, including hypertensives with diabetes mellitus (4) or with renal insufficiency (5), seem to be particularly well served by reduction of blood pressure to optimal levels.

Published guidelines for managing hypertension, both in the United States (5) and internationally (6), have endorsed the desirability of tight blood pressure control in appropriate patients. But despite these widely disseminated recommendations, clinical practice appears to lag far behind. According to the National Health and Nutrition Examination Survey (7), only about half the hypertensive people in the United States are receiving treatment, and of these, fewer than half (approximately 24% of all hypertensives) have their blood pressures controlled to 140/90 mm Hg or below. In all likelihood, only about 10% of hypertensive individuals have blood pressures maintained at the even lower optimal levels. Who is to blame? Suggested explanations include poor patient compliance with treatment, problems with access to health care or affordability of treatment, and physician knowledge and attitude to treatment (8). To be fair, it is often genuinely difficult to treat hypertension aggressively enough to reach optimal blood pressures goals, and complex regimens of drugs in high doses are frequently required (3).

Two recent studies cast light on differing aspects of this issue. One study, carried out in a Veterans Affairs (VA) medical setting, emphasizes potential problems in how physicians approach hypertension therapy (9); the other, a report from the Framingham Heart Study, looks at the long-term benefits of hypertension treatment for a particular population (10). Of course, both the VA population and the Framingham population have special characteristics that may, to some extent, limit the generalizability of conclusions from these studies, but the findings are of interest nonetheless.

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Key Words: Pathogenesis of hypertension, treatment of hypertension, clinical trials, physician practices.

A total of 800 hypertensive men (mean age: 65) were studied at five VA sites in New England during a 2-year period (9). A technique known as recursive partitioning, based on the probability that a variety of clinical and demographic variables in these patients would prompt an increase in treatment, was used to create a measure of "treatment intensity" in each patient, which in turn could then be associated with blood pressure control. At the outset, despite an average of six hypertension-related visits per year, 40% of the patients had blood pressures over 160/90 mm Hg. For clinic blood pressures of 155/90 mm Hg or higher, treatment was increased at 25.6% of visits; when systolic blood pressure was 165 mm Hg or higher (with diastolic blood pressure below 90 mm Hg), treatment was increased in only 21.6% of cases. Overall, changes in treatment occurred at 6.7% of visits, and generally were prompted by increases in blood pressure, the presence of coronary heart disease, and a previous record of changing treatment for that particular patient. Increases in therapy did not appear to be stimulated by the presence of other target organ changes or cardiovascular risk factors, or by patient demographics. Not surprisingly, patients with more intensive therapy for their hypertension achieved significantly lower blood pressure values.

There were insufficient data to assess the effect of patient compliance with therapy; unfortunately, pharmacy-dispensing records and comments in the patients' progress notes did not appear helpful in explaining the study findings. Moreover, in the VA setting, there is ready access to health care and drug therapy, usually at no cost to the patient. It is clear, however, that patients with higher blood pressures at a given visit tended to be brought back sooner than usual for a return visit, so it could be argued that many of the physicians involved, even when hesitant to adjust treatment, at least showed some sensitivity to the problem of poor blood pressure control. Despite this, the investigators concluded that "many physicians are not aggressive enough in their approach to hypertension."

The Framingham Study recently examined data on blood pressure, antihypertensive treatment and electrocardiographic (EKG) left ventricular hypertrophy during a 40-year period (1950–1989) in 10,333 people aged 45 to 74 (10). During this time, the prevalence of high blood pressure levels (systolic blood pressure of 160 mm Hg or higher or diastolic blood pressure of 100 mm Hg or higher) was reduced from 18.5% to 9.2% in men, and from 28% to 7.7% in women. At the same time, the use of antihypertensive medications in this population increased from 2.3% to 24.6% in men and from 5.7 to 27.7% in women. Based on rigorous EKG criteria, the prevalence of left ventricular hypertrophy during this period was reduced from 4.5% to 2.5% in men, and from 3.6% to 1.1% in women. In considering these results, though, it should be remembered that the Framingham cohort, knowing that it was under continuing scientific scrutiny, might have behaved somewhat differently than populations elsewhere.

The authors have interpreted these clear trends as indicating that increased use of antihypertensive medications has decreased the prevalence of hypertension, thereby reducing the prevalence of left ventricular hypertrophy in this community. Since left ventricular hypertrophy is known to be a strong predictor of major cardiovascular endpoints (11), the authors have boldly gone on to conjecture that this sequence of trends can explain the progressive reduction in cardiovascular deaths observed in the general population since the late 1960s. In addition, the authors suggest that the benefit of treatment may result from decreasing blood pressures at the higher end of the hypertension spectrum; this may well be true, though recent prospective trials suggest that modest blood pressure decrements in the lower hypertensive ranges also appear to confer benefits (3).

These reports from New England point out two interesting facts about our management of hypertension. On the one hand, the observations in Framingham provide reassurance that antihypertensive therapy in the community appears to be reducing the prevalence of hypertension and the incidence of serious cardiovascular events. But the VA findings indicate that physicians are still not able to fully achieve optimal or even, in many cases, remotely acceptable blood pressure goals. Newer, more efficacious antihypertensive drugs, with minimal side effects, should prove helpful in improving blood pressure management. Evidence from recent randomized clinical trials should provide a further spur to the outcomes benefits of aggressive antihypertensive therapy.

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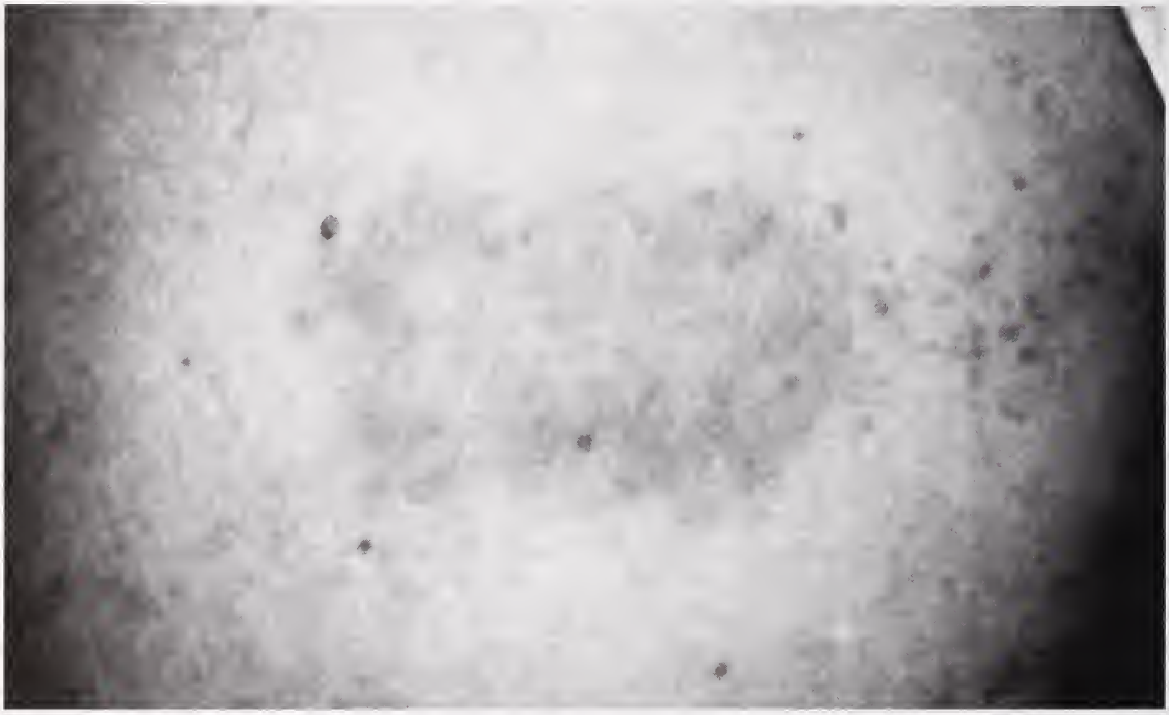
Dermatology Notes

Vitamin K Reaction



INTRAVASCULAR or subcutaneous injection of Vitamin K has been associated with a number of cutaneous manifestations. This eczematous reaction resulted from a subcutaneous injection of Vitamin K.

—Albert M. Lefkovits, M.D. and Mark G. Lebwohl, M.D.

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THEME ISSUE
GASTROENTEROLOGY AND HEPATOLOGY AT THE MOUNT SINAI HOSPITAL 1852–2000 — PART 2

Jeremy Hugh Baron and Henry D. Janowitz, guest editors

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Inflammatory Bowel Disease up to 1932

Jeremy Hugh Baron, D.M., F.R.C.P., F.R.C.S.

Abstract

Inflammatory bowel diseases have been a major interest of generations of Mount Sinai Hospital gastroenterologists. Although clinical descriptions of diarrhea with or without blood go back thousands of years, clear distinctions between enteritis and ulcerative colitis were possible only in the 19th century. At that time, many case reports were published of, in retrospect, classical regional enteritis. The term "ulcerative colitis" dates from 1888; the introduction of the electric sigmoidoscope soon after made it possible to make proper diagnosis of ulcerative colitis and distinguish it from infective dysentery, membranous mucous or catarrhal colitis, and nervous diarrhea. Doctors at The Mount Sinai Hospital adopted this diagnostic approach in the 1870s and 1880s, and were particularly interested in patients with tuberculosis-like ileocecal disease without tubercle bacilli. Articles were written by Weiner in 1914, Moschcowitz and Wilensky in 1923 and 1927, and Goldfarb and Suissman in 1931. Dr. A.A. Berg, in 1925, encouraged his assistant Leon Ginzburg to conduct a study of the inflammatory granulomatous diseases of the bowel, when Ginzburg and Gordon Oppenheimer were working in Dr. Paul Klemperer's laboratory. Initial reports came in 1927 and 1928, but Ginzburg and Oppenheimer "in conjunction with Dr. Burrill B. Crohn" presented a definitive paper, "Non-specific Granulomata of the Intestine," on May 2, 1932, to the American Gastro-Enterological Association. On May 13, 1932, Dr. Crohn presented a paper on "Terminal Ileitis" to the American Medical Association; this was published later that year with the title "Regional Ileitis: A Pathologic and Chronic Entity," under the authorship of Crohn, Ginzburg and Oppenheimer. **Key Words:** Inflammatory bowel disease, ulcerative colitis, regional enteritis, Crohn's disease, history.

INFLAMMATORY BOWEL DISEASES are the Mount Sinai gastrointestinal specialty par excellence, because of their high incidence among Jews, and because of the contributions of generations of Mount Sinai gastroenterologists to their diagnosis and treatment. The history of these diseases has often been reviewed (1 – 10), but their etiology and pathology are unclear, their management remains empirical, and the origins of their description are still controversial.

It is particularly useful to determine when particular diseases first appeared in human history, because the circumstances of their emergence may provide clues to their pathogenesis. This process is easier for bone or tooth disease, which may be traced in skeletons over thousands of years, but for internal disorders one needs more contemporary evidence from autopsies, laparotomies, and histologic and microbiologic examinations.

Enteritis in Europe

Clinical descriptions of acute and chronic diarrhea with or without blood go back thousands of years. Most of these symptoms may have been due to acute bacterial infections, whether self-limited, progressive, or fatal. However, autopsies were unusual before the 16th century, only becoming common in the 18th and routine (in certain hospitals) in the 19th century (11). Histology became available early, and microbiology later, in that century.

The hospital of S. Maria Nuova in Florence allowed dissections not only by Leonardo da Vinci (for his anatomical studies) but also by Antonio Beneviene (1443 – 1502), for comparison

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with the clinical course of his deceased patients. Of his 15 autopsies published posthumously (12), a nun with chronic intestinal obstruction ("XXXIV") had "intestines contracted by a thick callus" (possibly carcinoma rather than enteritis). "XLV" was a kinswoman with chronic recurrent flux of the bowels; the condition was cured "instantly" by a Dominican friar and showed no recurrence in a three-year follow-up [irritable bowel syndrome?]. "XCV" had "gripes in the intestines, called by the Greeks *dysenteria* . . . apt to ulcerate the lining of the intestines and thus the excrement comes down bloodstained and mucous." Both he and "XCVI," with similar symptoms, and in addition wasting and fatality with "entrails . . . internally eroded," may have had chronic dysentery or ulcerative colitis.

Autopsies were performed on the eminent, particularly royalty, in whom acute illness and death often raised suspicions of poisoning. Moreover, the previous medical events of monarchs were recorded, sometimes daily, and some of these records have survived. Thus, Louis XIII is known to have been prone to attacks of diarrhea for decades, with fever and a rectal abscess that discharged spontaneously. In 1642, he had bloody diarrhea, fever, abdominal pain and a perianal abscess or fistula; he died the following year, at age 42. Autopsy showed ulcerated small and large bowel, with abscesses and fistulas compatible with ileocecal tuberculosis or regional enteritis (13).

In 1761, Morgagni (14) reported a similar history in a man of 20 who had "mesenteric lymphadenopathy, . . . erosions, ulceration and perforation of the extremity of the ileum and the nearest point of the colon to the extent of two hands breadth." Again, retrospective precise diagnosis is impossible. Matthew Baillie's 1793 *Morbid Anatomy* (15) describes intestinal inflammation, more common in the large intestine, with thickened mucosa, ulcerated, sometimes tattered to shreds with perforation, penetration or fistula, all to be distinguished from cancer, with thick-walled, ulcerated mucosa, narrowed lumen, and dilated bowel cephalad. Some of these patients may have had regional enteritis rather than tuberculosis or cancer. Recently it has been suggested that Sir William Johnson (1715–1774), superintendent of Indian Affairs for the Six Nations, had inflammatory bowel disease with sclerosing cholangitis, arthritis and uveitis rather than alcoholic cirrhosis (16).

More convincing is Combe's Mr. Georges, in whom "The lower part of the ileum as far as the colon was contracted, for the space of three feet, to the size of a turkey's quill. The colon had three constrictions, one about three inches long at the distance of seven inches from the cecum, a second about one inch long at the distance of four inches from the former, and a third not quite half an inch long at the distance of three inches from the last" (17).

Crohn (2) recalled that as a medical student in 1907 he was asked to "skip the chapter on diseases of the small intestine in the *Osler Textbook of Medicine*, since only tuberculosis of the small bowel was recognized." Crohn's recollection is not confirmed; while Crohn may have been told to skip that chapter, the relevant section of the 6th edition (London and New York, 1905) discussed not only tuberculosis but also catarrhal enteritis, the celiac affection, sprue, diphtheritic or croupous enteritis, phlegmonous and ulcerative enteritis, intestinal ulcers and syphilis.

As early as 1828, Abercrombie (18) had devoted six sections of his book to mucosal diseases of the intestine: active, chronic, symptomatic ulceration, treatment, in infants, and incidental to other diseases. Abercrombie also distinguished between diseases of the rectum and colon (whole or part) and those of the ileum. Perhaps twenty of his case reports in this and subsequent editions would today be diagnosed as regional enteritis. One girl of 13 had ileocecal inflammatory thickening with skip lesions. Other patients had involvement of various parts of the small intestine, especially the terminal ileum, as well as various parts of the colon; some lesions had perforated. Some of the illustrations in Cruveilher's *Anatomie Pathologique* may represent regional enteritis (19); the strictured skip lesions from pylorus to rectum in Lever's patient at Guy's Hospital (20) may indicate the same condition. Bristowe (21) reported ulceration from the lower jejunum to the colon, with an ileal stricture, a perforation and an ileo-ileal fistula.

Wilks performed thousands of autopsies at Guy's hospital in London, and it is possible to trace, in successive editions of his *Lectures* (22–24), the evolution of his classification of inflammation of the bowel. In the first edition, in 1859 (22), he distinguished between enteritis, tuberculosis, caecitis, typhlitis, colitis and epidemic dysentery. In the same year, his forensic autopsy (25) suggested that a woman had not in fact been poisoned by her bigamist doctor husband, since the inflammation of the last 3 feet of ileum and ulceration of the whole large intestine to the rectum were more likely to have been primary, acute, non-epidemic dysentery, of which Wilks had seen only two other such cases in his

3000 autopsies. Was this regional enteritis (26) or even some drug-induced ileocolitis (27)? In his second edition (23), however, Wilks expanded the section on colitis and described local acute ileitis with inflammation of the whole wall, and at last, with microscopy available, the whole tissue charged with "pyoid corpuscles" (granulomas). These sections were not changed in the final edition (24). As microscopy became more routine, strictures at the ileocecal valve could be declared neither tuberculous nor carcinomatous, but merely chronically inflamed (28). In 1889, Fenwick (29) devoted the whole of his second lecture to non-malignant stricture of the ileocecal valve, but no microscopy was reported.

Probably the most scholarly attempt at documenting the existence and frequency of regional enteritis before 1900 was made by Fielding in a doctorate thesis for Cork in 1970, "An Enquiry into Certain Aspects of Regional Enteritis" (30). He searched the *Transactions of the Pathological Society of London* for 1850–1899 and tabulated 31 cases he considered probable regional enteritis; 4 had small intestine disease, 15 large bowel involvement, and 12 had both small bowel and colon affected (31). He even identified 25 possible additional cases (one ileal, 17 large colonic, 7 ileocolonic). Fielding then repeated this sampling for Dublin over the same 50 years, reviewing the *Dublin Quarterly Journal of Medical Science, Proceedings of the Pathological Society of Dublin* and the *Dublin Hospital Gazette* (32). He found 29 cases (including five from the 1840s), with 6 involving small bowel, 8 large intestine, and 14 both, fully supporting his conclusion that regional enteritis was not exclusively a 20th century disease (33).

Fielding was careful to point out that these retrospective diagnoses were his own. I would certainly accept his analysis of the probable diagnosis for Abraham Colles's "Organic Stricture of the Rectum" (34), in view of the perianal inflammation and fistulas, the rectovaginal and rectovesical fistulas, and the autopsy reports of non-ulcerated thickening of all coats of the intestine except the peritoneal tunic. In another case, described by Redmond (35), I agree with Fielding's interpretation that the painful swelling in the extremities was not due to acromegaly, in view of the normal face and skull. While the painful swelling in the extremities is more likely due to hypertrophic osteoarthropathy, I would still be reluctant to attribute the affliction to inflammatory bowel disease, because it preceded the diarrhea by 10 months, which (though possible) is unusual.

Some of Mayo Robson's (36) seven cases of chronic intestinal tuberculosis (photographs of specimens are provided for the first time in the 1902 article) were probably non-tuberculous giant cell granulomas. Six years later, in 1908, Robson reported patients with self-resolving abdominal tumors simulating malignant disease; some of them probably had diverticular disease and others "chronic infiltrating colitis" (37). Other accounts of idiopathic chronic inflammatory disease of the large or small intestine were reported from: England (38–40), France (41–43), Germany (44–51), Hungary (52), Italy (53), Japan (54), the Netherlands (55), Poland (56), Russia (57), and Scotland (30, 58). Some of these cases of intestinal inflammation were probably not idiopathic but pericolitis (59), diverticulitis (60) or post-appendectomy abscess (61). By 1939, Shapiro was able to give 289 citations on regional ileitis (1).

Enteritis in the U.S.

The first American contribution to the study of chronic inflammatory bowel disease was in 1901 by Lartigau, who described chronic hyperplastic tuberculosis of the intestines (62). By then, microscopy was able to identify the hidden bacilli in his and similar cases, but Lartigau raised the possibility of non-tuberculous causes of granulomas.

A steady stream of similar publications came from many parts of the U.S. in the 1920s. Jones and Eisenberg (63) from Cleveland removed a hard ileocolic mass which turned out to be simple inflammation and not carcinoma. Coffen (64) from Portland, Oregon, treated a young man who in nine years needed three operations for granulomatous tumors causing intestinal obstruction. Horsley (65) reported three patients from Richmond, VA whose resected specimens showed granulomas which he thought were tuberculous until that diagnosis was rejected by A.C. Broders of the Mayo Clinic. In 1926, the Cabots (66) reported a case from Boston. In 1930, Bargen and Weber (67) reported 23 cases of regional, segmental, localized or migratory ulcerative colitis seen over a period of 18 months at the Mayo Clinic; in the absence of histology it is not possible to be sure whether they were true ulcerative colitis or regional enteritis. In 1931, Mock (68) from Chicago described six cases: "Infective granulomata are far more frequent than the literature on this subject would lead one to believe," and he chose his complex subtitle "Non-specific chronic tumor-like productive inflammations of the gastrointestinal tract," after consulting eight pathologists and seven surgeons. Golob (69) from Sydenham Hospital, New York, resected the cecum for a hypertrophied ileocecal valve; granulomas and giant cell infiltration were found on histology by D.C. Balfour of the Mayo Clinic, who used a fourfold classification for such operative specimens: tuberculosis, diverticulitis, pyogenic, nonspecific granulomas.

Colitis

Throughout the 19th century, there was increasing recognition that there were non- infective causes of colonic ulceration. When Allchin, in 1885, reported a typical clinical and autopsy case of "follicular ulceration of the colon," he pleaded that "the term dysentery . . . should not at once be applied in an adjective form to any diarrhea depending upon ulceration of the colon, when the factors for the production of the specific disease are, so far as we can recognize, wanting" (70). Wilks (22) had referred to a ragged ulcerative surface in colitis, but the term "ulcerative colitis" was coined in 1888 by Hale-White (71), who later (72) distinguished (without sigmoidoscopy) 60 cases of "membranous colitis" or "mucomembranous entero-colitis," terms he preferred to mucous colic, glairy enteritis, glutinous diarrhea, tubular diarrhea, mucus affection of the intestine or intestinal croup. Hale-White's patients passed membrane or mucus or (rarely) blood and were all constipated; many had constant or acute pains, symptoms we should probably label today as irritable bowel syndrome. The 60 were mostly nervous, neurasthenic, hypochondriacal or hysterical.

Clarity came in the early 1900s from a surgeon, Lockhart-Mummery, at St. Mark's (the London rectal hospital). He stated quite simply, "The most important advance in our knowledge of these cases has been due to the invention of the electric sigmoidoscope" (73). Among his 36 patients Lockhart-Mummery saw definite inflammation in 24 and found a tumor in 7. In 4, he saw excess gelatinous mucus on a thick edematous, but still shiny, mucosa; he called the condition "chronic hypertrophic catarrh" (74). His sigmoidoscopic distinction between this chronic hypertrophic catarrh and true colitis led him to emphasize that colitis was not a neurosis but a disease with visible structural lesions. In 1907, he used the term "sigmoiditis" to indicate that with a sigmoidoscope he could be sure only that the colitis involved the rectosigmoid, and he could not know whether the whole colon was involved (75).

Two long meetings at the Royal Society of Medicine in 1909, taking up almost one hundred pages in the *Proceedings* (76), analyzed 333 patients with colitis over a twenty-year period from nine of the great voluntary hospitals in London, and again Lockhart-Mummery rightly complained that the internal medicine specialists did not use sigmoidoscopes. One of the chairmen, Sir Patrick Manson, still regarded ulcerative colitis as merely a dysentery, a position still proposed by Sandwith as late as 1914 (77).

The Mount Sinai Hospital

The annual reports of The Mount Sinai Hospital from 1857 tabulate the diagnoses assigned to diarrheal illnesses, such as Ascaris (1860) and Taenia (1864) and, in 1864, catarrh of the intestine, or gastrointestinal catarrh. These diagnoses, together with dysentery (1868) or (gastro-)enteritis (1869), remained the most common for digestive diseases after gastric catarrh.

Colitis first appears in these reports in 1876. In 1879, dysentery is divided into acute and chronic, and enteritis into acute, chronic and follicular. Colitis was further classified as membranous (1887), acute and chronic catarrhal (1888), acute and chronic ulcerative colitis and acute proctitis (1890), subacute (1892) and hemorrhagic (1897). Tuberculous enteritis was reported in 1888. By 1898, mucous colitis with neurasthenia was recognized, and in the following year membranous/croupous and necrotic colitis were described, as well as enterocolitis. In 1901, Lilienthal reported a total colectomy for "hyperplastic colitis" with ileorectal anastomosis (78).

There are occasional references in *The Mount Sinai Hospital Reports* to patients who in retrospect may have had regional enteritis. For example, in 1904 (2nd Surgical Service, p. 234), there was a patient with "Chronic Intestinal Obstruction and Stricture of Ileum" who was operated upon and survived. In 1905 (1st Surgical Service), there was a patient with a "Stricture of Ileocecal Valve (Polypoid Colitis)" who died, but no details are available. In 1906 (2nd Surgical Service), there was a patient with a tumor of ileocecal junction who died without an operation having been performed.

Tuberculosis or Granulomatous Disease of the Intestine

Mount Sinai's first published contribution to the study of ileocecal inflammation came in 1914. During a 13-year period, Weiner (79) collected 10 cases of ulcerative enteroperitoneal and hypertrophic ileocecal tumors, all of which were attributed to tuberculosis. However, pathological details were minimal and no tubercle bacilli were found, either in the resected bowel or in sputum, so that some or all of these patients may have had regional enteritis. Definite tuberculomas of the cecum with tubercle bacilli in the tissue sections, however, were still being found at Mount Sinai in the 1920s (80).

The landmark publication from Mount Sinai was in 1923 by Moschcowitz and Wilensky (81), who labored, however, under the impression that the disease had not been reported before 1908 or outside Europe. Their first patient had strictures initially of the cecum and later of the ileum. Detailed histology by O.B. Hunter showed giant cell granulomas, which were also found in the resected masses of the other three cases (in ascending colon, splenic flexure, ascending colon). Moschcowitz and Wilensky too were convinced that most patients diagnosed with hyperplastic tuberculosis of the intestine simply had granulomatous disease. They emphasized the increasing number of cases being published, "so that it is safe to say the malady is not at all a rare one." Three years later Wilensky and Moschcowitz reported another case (82). A young man of 18 presented first with a right iliac fossa abscess following a perforated appendix; the right hemicolectomy specimen showed inflammation only in the ascending colon. He was well for five years, until he had a recurrent right iliac fossa mass of thickened, coiled small intestine. The resected mass showed that only the terminal ileum was inflamed, with the now typical granulomatous inflammation. The Mount Sinai authors were satisfied that granulomatous disease of the intestine (small and/or large) was the undoubted cause of "many if not a majority of the cases of so-called 'hyperplastic tuberculosis of the colon,'" but this paper seems to have made little impact and was rarely if ever cited before 1932, even by Mount Sinai investigators in this field.

As late as 1931, tuberculosis of the intestines was still being diagnosed radiologically at The Mount Sinai Hospital. Goldfarb and Sussman (83) were well aware of work at Mount Sinai (81, 82, 84) indicating "that chronic, non-specific, infectious granuloma of the colon can resemble very closely chronic, hyperplastic tuberculosis, clinically, roentgenologically and pathologically." Two of their cases had pulmonary tuberculosis, and both laparotomy and histology of the resected colon were reported as tuberculosis. However, their third case of "tuberculosis of the colon," with narrowing of the terminal ileum and skip lesions in the colon, had a normal chest X-ray, and final diagnosis was uncertain in the absence of laparotomy.

Only one of 4,800 autopsies at The Mount Sinai Hospital between 1926 and 1938 revealed primary intestinal tuberculosis, and this case had progressed to the miliary stage (85). In the same 12-year period, seven other cases were "substantiated" as tuberculous in surgical resection specimens (although only two showed acid-fast bacilli), while 130 specimens were diagnosed as nonspecific granulomatous regional ileitis and segmental colitis. Presumably, one of the specimens re-examined by Crohn and Yarnis in 1940 was a resected ascending colon stricture reported by Klein in 1936 (86) and confidently diagnosed as hyperplastic ileocecal tuberculosis, even though no tubercle bacilli could be found. Crohn and Yarnis concluded:

> The relative scarcity of intestinal tuberculosis, as of today, in comparison with the nonspecific forms, may be explained on several grounds. The primary reason consists in the fact that all these nonspecific forms, like ileitis, were previously regarded as tuberculosis, though the scientific proof was carelessly lacking or was rarely sought for. By eliminating the nonspecific forms from all right lower quadrant granulomata, we find, on analysis, that very little remains as true tuberculosis. In the second instance, primary intestine tuberculosis, if ever a frequent disease, seems now definitely on the wane . . . bovine herd infestation by tuberculosis has been almost completely eliminated. (85)

Yet intestinal tuberculosis (proven by acid-fast bacilli in the resected specimens) was still occasionally a surprising finding at laparotomy from the 1930s to the 1950s at Mount Sinai, disproving preoperative diagnoses of granulomatous ileitis, cecal carcinoma, retroperitoneal sarcoma, pancreatic carcinoma, granulomatous jejunoileitis, acute appendicitis and metastatic carcinoma (87). Moreover, by the 1950s effective antituberculosis chemotherapy was available to arrest the tuberculosis (87).

The Two Mount Sinai Presentations of May 1932

In May 1932, there were two relevant presentations by Mount Sinai staff at national meetings in the U.S.A.; both presentations were sponsored by Crohn. On December 11, 1931, Crohn had written to the American Gastro-Enterological Association:

> I have an important scientific contribution I would like to present before the American Gastrological Association next May. I have discovered, I believe, a new intestinal disease, which we have named Terminal Ileitis. I should like to present the facts before the Association in connection with the general subject of Benign Granulomata of the Intestinal Tract. I am submitting the abstract on a separate sheet. My very kind regards.
>
> P.S. I should like the name of Dr. Leon Ginzburg associated with mine, by invitation, at the reading of the article. B.B.C. (88)

The first of the two presentations was read by Ginzburg at Atlantic City on May 2–3, 1932, to the American Gastro-Enterological Association. This presentation was ultimately published "in conjunction with Dr. Burrill B. Crohn" in the 1932 *AGA Transactions* (84), and subsequently in the *Annals of Surgery* (89) in expanded form in 1933. The second presentation was given by Crohn on May 13, at New Orleans, to the Section on Gastro–Enterology and Proctology of the American Medical Association. In due course, it was published in *JAMA* as by Crohn, Ginzburg and Oppenheimer (90) (see Fig.); however, the Section Program in *JAMA* April 9, 1932 states "Terminal Ileitis: Its clinical manifestations (Lantern Demonstration). BURRILL B. Crohn, New York. Discussion to be opened by JOHN E. JENNINGS, Brooklyn." (91)

Page 152 of the Program given to those at the 1932 AMA meeting included the following:

> Terminal Ileitis: Its Clinical Manifestations (Lantern Demonstration). Burrill B. Crohn, New York.
>
> **Abst.** — Report of fifteen [Editor's note: 14, in the published papers] cases of a disease hitherto undescribed in the literature, except for sporadic references to incompleted observations. The disease constitutes a clinical entity and is characterized by a chronic and progressive course, a necrosing and cicatrizing inflammatory lesion of the terminal 8 to 12 inches of the ileum, and diarrhea. Another pathognomonic feature is fistula formation; such fistulas lead usually from the ileum to various parts of the colon and occasionally to the anterior abdominal wall. The patients have all been operated on; death from peritonitis resulted in two cases, the remaining patients all being alive and well. No etiologic factor has been found as a cause of the disease. It is definitely not neoplastic nor bacterial; it may be a disease of the vascular supply of the mesentery.
>
> Discussion to be opened by W.C. Chaney, Memphis, Tenn., and John E. Jennings, Brooklyn.

The Section Minutes (92) state that "Dr. Burrill B. Crohn, New York, read a paper on 'Terminal Ileitis, its clinical manifestations' which was discussed by. . . ."

The AGA Paper

Ginzburg was A.A. Berg's house surgeon in 1925, and for the next five years his adjunct and his assistant in private practice (93). During these years, at Berg's suggestion (94), Ginzburg made a specific study of the inflammatory granulomatous diseases of the bowel. In 1927, he and Beller (95) reported 12 cases of non-metallic perforating intestinal foreign bodies (6 fish bones, 5 chicken bones, 1 wooden toothpick) inciting an inflammatory granulomatous reaction with multinuclear giant cells. Three patients had presented with intra-abdominal tumors, but in each the mucosa and submucosa were normal, as distinguished from the cases of Tietze (50) in Germany and those of Wilensky & Moschcowitz at Mount Sinai (81, 82). In 1928, Ginzburg, with Eugene Klein (96), described five cases of late fibrotic intestinal stenosis following strangulated hernia, producing tubular or annular strictures, presumably ischemic, in which the submucosa was thickened and the mucosa often ulcerated.

Ginzburg and Oppenheimer then searched back to 1920 for excised inflammatory masses of the large or small intestines (excluding sigmoid diverticulitis) and found 52 such cases. Together with Drs. Gross, Klemperer, Otani and Antopol, they restudied the pathology. They described six groups with detailed case histories in the 1932 paper (84) but with no radiographs, pathological photographs or references; these parts of the case reports appear in their December 1933 paper (89), but without the case histories or the discussion. The six groups were as follows.

1. Extra- or peri-intestinal granulomata secondary to sealed-off perforations of the bowel. These ten cases were akin to those in their 1927 paper (95).

2. Granulomata secondary to known vascular disturbances of the gut. These five were probably not those in their 1928 paper (96).

3. Localized hypertrophic ulcerative stenosis of the terminal ileum. Of these 14 patients, 12 had been studied by Ginzburg and Oppenheimer, and two added by Crohn (93). There were four modes of presentation:

   a. simulating acute appendicitis, but with the terminal ileum abnormal and the appendix normal;

   b. symptoms of ulcerative enteritis, low grade diarrhea, weight loss, colic, anemia;

   c. symptoms of chronic incomplete small intestinal obstruction;

   d. chronic intractable fistulae.

   Tuberculosis was excluded by all available tests, and indeed only six cases of localized hypertrophic tuberculosis had been resected at Mount Sinai in the previous ten years, as opposed to 18 of the non-specific variety.

4. Localized hypertrophic colitis with or without low-grade generalized colitis (cecum/ascending 5, rectosigmoid 3, midsigmoid 1, sigmoid/descending 3). Some cases also had ileal and perianal diseases.

5. Simple penetrating ulcers of the colon.

6. Lesions secondary to inflammation of the appendages of the bowel, such as appendicitis, diverticulitis, typhlitis.

The discussants of the Ginzburg and Oppenheimer paper at the AGA were all internists (84). Bockus thought these lesions rare, and wondered "whether in some individuals with undue ptosis the factor of disturbed circulation might be a contributing factor in the production of terminal ileitis by twisting the (ileo-colic) artery or by undue stasis in the vein (terminal branch)." Alvarez, however, thought otherwise: "I have long felt that there must be such a thing as terminal ileitis. I think it is a fairly common disease." Crohn re-emphasized this point:

> One may mistakenly think that we are demonstrating a very rare lesion. Now that we are aware of the clinical condition, we are seeing at Mount Sinai at least three, four or five cases a year. We had one case two months ago and I have now a case which will be operated upon on our return. At a session of the New York Surgical Society about four weeks ago, one of the members of that association presented a case of granuloma of the terminal ileum; to my surprise he was showing this same condition. The chairman asked for general discussion; six surgeons of large experience with abdominal conditions discussed the subject. Several men recounted having seen a case six years ago or twelve years ago, upon which he had operated with good result. These were surgeons with wide experience; several of these surgeons in the course of a lifetime had seen such lesions, but had apparently not been able to recognize or identify the underlying pathological process. (84)

The Ginzburg and Oppenheimer AGA 1932 presentation is referred to by Ginzburg himself (97), in the 1933 *Annals of Surgery* publication (89). However, I can find no previous account, even by Ginzburg or Oppenheimer, that they were aware that Ginzburg's presentation in Atlantic City to the AGA was published in the annual *Transactions of the American Gastro-Enterological Association* for 1932 (84).

The AMA Paper

Fifty-five years after the event, Ginzburg related the following account (97):

> In the summer of 1931, Dr. Crohn spoke to me about 2 patients of his, upon whom Dr. Berg had operated for unusual lesions in the terminal ileum. He told me that he had been to the Path Lab to inquire about the nature of these lesions. There he was told that Ginzburg and Oppenheimer had already studied and described a similar series of cases. He told me that he had spoken to Dr. Berg, who wanted me to turn over to him (Dr. Crohn) the studies and the already written article for his (Dr. Crohn's) perusal. I gave him the already written article and that was the last I saw of it, until the actual publication appeared in the fall of 1932. By that time the original short, descriptive article, limited to the actual definition of the apparently new entity, had been almost submerged under the sections that had been added by Dr. Crohn. Its volume had more than doubled!

> In the spring of 1932, some members of the Mt Sinai Medical Staff noticed that on the program of the forthcoming annual meeting of the AMA, Dr. Crohn had listed an article on regional enteritis. It was also noted that the names of Leon Ginzburg (L.G.) and Gordon D. Oppenheimer (G.D.O.) who were known to be studying this same condition, were absent. A considerable to-do developed and rumors spread about this omission. Eventually, a group was informally chosen to investigate the situation. I am not personally privy to what actually went on, except that as a "subpoenaed material witness" I was pretty roughly handled by Dr. Berg, who chaired and dominated the committee. In any event, the eventual decision was that the names of Leon Ginzburg and Gordon D. Oppenheimer were either to be added and/or restored, as coauthors in the published article.

Ginzburg did concede:

> There is no doubt that Dr. Crohn "put regional enteritis on the map," so to speak. He popularized, publicized and spent much time, effort and travel on lecturing and spreading knowledge about it. His extensive collection of statistics gathered from his own practice helped clarify matters in the early days. (97)

Crohn's communication to the AMA had the title "Terminal Ileitis" (91, 92, 97) and was limited to the 14 patients of A.A. Berg, of whom 12 had been studied originally by Ginzburg and Oppenheimer's group (95) and 2 patients seen by Crohn and categorized as a distinct group which they called "localized hypertrophic ulcerative stenosis of the terminal ileum" (84, 89). The discussion was enthusiastic, with similar cases reported by Friedenwald (Baltimore), Hirschman (Detroit) and Bargen (Mayo Clinic): "This presentation would seem timely, for, with improved roentgen technique and more intensive study of intestinal disease, the condition may prove to be less [*sic*] common than it is now supposed to be. . . . I am wondering whether the designation 'terminal' is adequately descriptive. To some it has conveyed the meaning of agonal. Perhaps the modifying adjective 'regional' or some other word suggesting its localized nature, instead of the end, would be more suitable." The paper, as published in *JAMA* on October 15, 1932, was therefore entitled *Regional Ileitis* (90). Hirschmann questioned the statement that it was uncommon for a patient to have both ulcerative colitis and granulomatous ileitis, since he had "just such a case." In closing, Crohn did not address this especially important point.

Conclusion

The entity now termed "Crohn's disease" clearly has been reported in the medical literature for many centuries. However, I conclude that the Ginzburg and Oppenheimer AGA presentation in 1932 and subsequent papers (84, 85) were the definitive clinicopathological studies which established the entity of regional enteritis in both small and large intestine. Yet the earliest presentation made little impact, probably because it was delivered to a small, select audience at the AGA, could be read in 1932 only by the 100 members of the AGA in their *Transactions* (84), and did not appear in a journal of wider circulation until 1933 (89). Moreover, neither paper, i.e., the *AGA Transactions* or the one in the *Annals of Surgery*, was complete in itself, and both would have had to be read together and collated, which to my knowledge has never been done before. In both of these papers by Ginzburg and Oppenheimer (84, 89), there is a footnote: "The section on Localized Ileitis represents a joint study with Dr. Burrill B. Crohn." By contrast, the paper Crohn delivered at the AMA was to a wider audience, and ultimately appeared in print in the *Journal of the American Medical Association* (90) earlier than the previously mentioned papers.

My conclusion is based on an examination of all 3 papers, Crohn's 1932 statement (98), interviews (99, 100), and memoirs (101), Ginzburg's interview (102) and historical perspective (97), as well as Winkelstein's interview (103), all of which (except the first) were written decades after the events of 1931 – 1932 (see Appendix).

Epilogue

In 1933, a paper appeared with the eponymous title ". . . Regional Ileitis (Crohn). . ." (104) and another Mount Sinai eponym was born. Seventy years later, it is probably more widely used than other Mount Sinai eponyms, such as Koplik spots, the Hollander and Schick tests, or Buerger's or Tay-Sachs diseases.

Appendix

Statement by Dr. Burrill B Crohn, 1932 (98):

Following is a statement aiming to explain the relationship between Dr. Leon Ginzburg and myself on the subject of "Terminal Ileitis":

During 1929–30 I was interested in three private cases of intestinal disease. These cases were operated upon by Dr. Berg in 1930–1931. They were all three instances of unusual pathological processes which led for the first time in our experience to the recognition of what we later named "Terminal Ileitis." Shortly thereafter Dr. Berg operated upon two more cases, confirming the fact that we had run across an interesting clinical entity. I proposed to Dr. Berg a joint publication on the subject. He preferred that I should associate with myself a younger man.

For several years previous to our clinical findings, Dr. Ginzburg and Dr. Gordon Oppenheimer had been studying benign granulomata of the intestinal tract. These were pathological studies and included a collection of general benign inflammatory processes of the intestine. Dr. Ginzburg was therefore the logical man to associate with me. The proposition to study and to write, from me to Dr. Ginzburg, was accepted by him, and a completely harmonious relationship has existed from that day until this week.

Among Dr. Ginzburg's general collection of specimens of intestinal granulomata was one which corresponded very definitely with the pathological picture of Ileitis. This specimen had been described in detail in a paper written by Dr. Ginzburg on intestinal granulomata, which unpublished paper and specimen I was privileged to see. The work progressed smoothly; fourteen clinical cases were collected, seven of these being old cases and old pathological specimens which had been unclassified, but which now in the light of our new grouping, took definite form and were now clearly recognized as examples of this same disease.

Publications

It was suggested by Dr. Ginzburg in November or December 1931 that we write a joint preliminary paper and publish it quickly in the *Annals of Surgery*. This was suggested because I had been free in showing the specimens to prominent medical men, visiting the hospital, all of whom had stated that they had never seen a like process in clinical medicine. I invited Dr. Ginzburg to my home for dinner and to write the paper. We divided the work, he to write the pathology and the surgical treatment of the disease, and I to write the clinical description. I finished my share within three days and then waited so long for Dr. Ginzburg's contribution, that it finally became evident that it would be too late for any publication before the annual meetings. We decided that the subject was of a sufficient importance to warrant fairly wide notice. I therefore reserved space on the program of the Gastrointestinal Section of the AMA Meeting in New Orleans. I personally was to go, at my own expense, and read that joint paper. I also arranged to have Dr. Ginzburg present the entire subject of benign granulomata of the intestinal tract before the American Gastro-Enterological Association, lending my name, so that be might be included "by invitation." This paper was to be a general paper on granulomata, but to deal prominently with ileitis. This was to be the first reading of that original paper by Doctors Ginzburg and Oppenheimer. I did not ask to be co-author in this paper. These were the two important national presentations. The Academy of Medicine Meeting of the Medical Section was an afterthought suggested by Dr. Baehr. Both names were to appear on the program, I as the member of the Section necessarily to read the paper. There were three local hospital presentations, two were in the course of Friday afternoon rounds, one by Dr. Ginzburg, one by myself; there was one presentation at the February Clinical Conference. This presentation was by Dr. Ginzburg with my knowledge and agreement, in fact, on my suggestion.

All these arrangements were apparently harmoniously made, and as far as I knew, harmoniously carried out. There were however, two possible slip-ups; one, the arrangements with Dr. Andresen, Secretary to the Section of the A.M.A., were made by telephone to Brooklyn. Apparently in the course of these several telephone messages, Dr. Ginzburg's name slipped by, at least as far as the preliminary program published in the April number of the A.M.A. Dr. Andresen assures me that the permanent program will only appear at the New Orleans session, and he cannot re-call whether Dr. Ginzburg's name is or is not on that program. The second slip was made by Dr. Pardee at the Academy of Medicine, which unfortunate occurrence was corrected by Dr. Pardee publicly at the meeting, and due apology made. The final manuscript bears the names of myself and Dr. Ginzburg, and in addition as a courtesy to the unfortunate Dr. Oppenheimer, his name has been included as co-author, though I have never seen nor spoken to Dr. Oppenheimer on this subject.

I should like to further state that very little question of priority, or of precedence or of privilege has ever arisen between Dr. Ginzburg and myself. I am convinced that any bad feeling arose from poor advice from some of his more radical friends. In submitting to the Committee the documentary evidence confirming my statements, I wish to say that I am perfectly satisfied with my own conduct in the matter. I feel that I never was under any compulsion to include Leon Ginzburg in this study, as I feel convinced that the identification and recognition of this not unusual clinical condition had been missed until I pointed it out. And I make this statement with the full knowledge that Dr. Ginzburg had described one specimen of ileitis in his paper on granulomata, that Eli Moschcowitz had seen a somewhat similar but not identified pathological condition in 1927, and that several surgeons of wide experience had at least operated upon one, or at most two cases, without having recognized or understood the nature of the pathological process. I invited Dr. Ginzburg to cooperate as a matter of harmony and courtesy, and to establish a harmonious link with the Pathological Laboratory, thus accelerating all processes.

I do not regret today that invitation, and feel, that I could continue to work harmoniously with Dr. Ginzburg if the subterranean and unknown faction that refuses to be named and refuses to come out in the open, would cease insinuating to him that someone is trying to wrong him.

In final proof of my spirit in the past under similar conditions, I submit reprints of the last several years. In nearly all my publications I have included younger men. In many of them I have put my name last. In one, the name of a medical student, Lionel Auster, who worked with me five to six years ago; in another publication from my clinic, from my own material, Sylvan Manheim appears as sole author, though I wrote the paper; and in many other similar conditions, I have always cooperated with younger men. (B.B. Crohn)

In 1965 Dr. Crohn recalled (99):

When I was a medical student at P and S, College of Physicians and Surgeons, Professor Evan Evans, Professor of Medicine, said when we came to the chapter on the small intestine in the textbook of medicine, "Gentlemen, we will skip the next chapter, since there are no recognized diseases of the small intestine, except tuberculosis."

In the laboratory at Mount Sinai, during the autopsies, Dr. Libman always insisted that the small intestine, not even to bother to open it and look into it. *[Perhaps Crohn meant to say that the small intestine should always be opened.]* In spite of that, we saw no diseases of the small intestine. We assumed that everything was intestinal tuberculosis.

I had a private case with a mass, with fever, with diarrhea and abdominal pain, but at this time we had new laboratory tests which the past generations didn't have. We had the Von Pirquet test for tuberculosis. We had the intradermal tubercular test. And now we had X-rays of the chest.

In this boy, all the tests for tuberculosis were negative. I said to Dr. Berg, "There is only one way to cure this boy, and that's to operate upon him." Whereupon Dr. Berg said, "I will not operate for intestinal tuberculosis. I was persuaded by Dr. Trudeau at Saranac to operate on five of this [type of] case for intestinal tuberculosis. Three of them died, and the other two I never heard from and I never want to."

So it took a great deal of persuasion on my part to talk Dr. Berg into resecting this case, into operating and resecting it. He did resect the case. When we opened it, we saw that it was something new, a granuloma. We went through every exhaustive test in the laboratory, including guinea pig inoculations, rabbit inoculation, watching over it for months, exhausting ourselves to try to find tubercle bacilli or the evidence of tuberculosis. And finally we said this was a non-specific disease.

At this time also Drs. Leon Ginzburg and Gordon D. Oppenheimer had been engaged independently in a study of granulomas of the body, of the abdominal cavity, intestines, liver, spleen, and anything else. They were doing pathological work, not clinical work. When we . . . I . . . had corralled fourteen cases using my private cases . . . the first three were private cases, using also ward cases . . . we found fourteen cases on which to publish the paper. And I suggested to Dr. Berg that he be the co-author with me, because he and I had done all the clinical work. He, in the graciousness of his personality said, "I think you should take Ginzburg and Oppenheimer as your partners. You can leave me out."

Ginzburg and Oppenheimer therefore became co-authors with me. The paper was read at New Orleans in the spring of 1932. It was immediately acclaimed. Strange that no one questioned the fact that a new clinical entity had been described. The Mayo people went home to Rochester, Minnesota. Shortly, I heard from them that they'd taken out and reviewed all the X-ray films of the past couple of years, and shortly they published, on the basis of old films which they had ignored and overlooked, their very large experience with ileitis.

John Cantor came home, got his film out, saw that he too had overlooked the X-ray picture of ileitis, and he said, "It looks like a string to me, a spasm in a string." It was on the basis of his remark, his published remark, that the demonstration of ileitis was called "a string sign." (B.B. Crohn)

In 1968 Crohn recalled (100):

Here is the case history of the first case of ileitis: The patient was admitted in 1929. A young man, 17 years old, with fever, abdominal mass and diarrhea. And I put down the diagnosis as "Tuberculosis" because it was the only etiologic agent that could cause this. The patient was readmitted in 1930. This time I left the diagnosis out because I couldn't determine it. He was readmitted the 3rd time in 1930; again the diagnosis: "Tuberculosis of the Colon, Hyperplastic Ileocecal Type," given oxygen intraperitoneal insufflation with improvement. Admitted the 4th time in 1931, he was operated upon. Now the old diagnosis of tuberculosis was out and the diagnosis became: "Terminal Ileitis, with resection of terminal ileum, cecum, ascending colon and of the transverse colon." And that was case number one of regional ileitis. And then, as I said in my book, we began to look for granulomas of the intestinal wall, because Dr. Leon Ginzburg and Dr. Eli Moschcowitz had studied granulomas in the laboratory as pathological specimens but without any clinical collaboration or correlation between the laboratory findings and clinical aspects of the cases; they were doing pure pathology research. It was my opportunity to combine pathology and clinical medicine, having had training in both disciplines. Dr. A.A. Berg and I then re-examined all the obscure cases of diarrhea with abdominal mass and with fistulas; very shortly we had the data on the first 14 cases. (B.B. Crohn)

In 1965 Ginzburg recalled (102):

This was in the mid-Twenties. From there, I suggested to Dr. Gordon Oppenheimer, who at that time was working in surgical pathology at the old laboratory, that we ought to keep an eye on these granuloma[s] of the bowels, and that we were interested in inflammatory tumors and strictures of the bowel. At that time we were interested in them mainly in so far as it would be possible to distinguish them from neoplastic diseases of the bowel.

I was an Assistant for Dr. Berg and on his service. We collected a series of these cases. Then we started to encounter something that we'd never seen before, and we couldn't make head or tail of it. It was a disease involving the distal ileum. Those cases all seemed to stop short right at the ileocecal valve. Most of them, in those days prior to radiological study of the small bowel, which was very primitive then, had been diagnosed as lymphosarcoma or carcinoma, and as a matter of fact there were a couple of cases that had sigmoidal ileofistulas. The deformity in the sigmoid was interpreted as evidence of carcinoma of the sigmoid and that's what patients were operated upon for.

In any event, we had a few of these specimens. And at the same time, we were very much interested in some chronic intractable fistulae that occurred after appendectomy, after what was supposed to be an operation for bad appendicitis. A great many of these patients had had local closures attempted, which were all failures, and some had had an ileocolostomy with exclusion, where they healed up, but we hadn't had any specimens.

Then one day a patient who had had intractable fistulae following appendectomy and drainage of an abscess, a resection of a segment of bowel was undertaken, again by Dr. Berg. And incidentally, Dr. Berg is the unsung hero of ileitis, because he resected every specimen on which the studies were made. In this case, he again resected the terminal ileum, and we were all aflutter, because when that specimen was opened, it looked just like the specimens that had previously been resected for what appeared to be tumors and obstructions in the bowel.

See, the original cases were operated on mostly for obstruction. That's what brought them to operation. These people had all had histories of diarrhea, etc. But this was the first case where a link was shown between the basic underlying pathology of these so-called post-appendicular fistulae, which we found not to be due to the appendix, since the appendix stump was quite healed over. It was in this case that we saw that these lesions had perforated in between the leaves of the mesentery, and that an abscess had formed intermesenterally first which had perforated secondarily.

So we hooked up these different types, and we defined four different types at that time: one, where patients presented themselves with signs of obstruction; then with signs of what you might call an enteritis; thirdly, those who had appeared as acute appendicitis or appendix abscesses; and finally, the ones that appeared as intractable fecal fistulae and intra-abdominal inflammation. And although now we just take it for granted, after all there was quite a bit of clinical diversity between an appendix, or an intra-abdominal inflammatory mass which drained interminably, and a patient who had an obstruction without any evidence of intra-abdominal inflammation, who had simply had symptoms of severe enteritis without any evidence either of obstruction or intra-abdominal inflammation.

About this time, Dr. Crohn had a couple of cases. We had, I think, six or seven different types of inflammatory diseases. We had excluded diverticulitis, because by that time it had been pretty well studied, but aside from that we had the ones due to foreign bodies, we had the strictures and so forth due to vascular impairment, we had this regional enteritis, which we had originally called segmental granulomatous disease of the bowel. Incidentally, although we didn't hook up the two, we also found cases of localized (. . . we called them hypertrophic) colitis, which is the same as the granulomatous colitis, but we didn't hook them up with the granulomatous diseases of the bowel. We thought that was something quite different. We also called attention in that paper to the fact that in some of these patients with the granulomatous localized hypertrophic localized colitis, this was also evidence of a diffuse colitis. This, too, had been brought out, I think at the Mayo Clinic, where they had some time ago reported the segmental hypertrophic colitises.

But the one thing that we called to the attention, struck the attention, was this regional enteritis, and Dr. Crohn saw a couple of cases of this type which had been operated on by Dr. Berg. Since his mind hadn't been to some extent beclouded by the other types of inflammatory diseases of the bowel, he picked this out, took it out of the ordinary group and described it by itself. We were originally going to describe it as one of the groups of inflammatory diseases of the bowel producing tumors or strictures. We didn't know the etiology then any more than we knew the etiology of colitis.

The paper first appeared; it was read by Dr. Crohn. The paper was written in different parts. The paper was written actually by Dr. Crohn and myself absolutely independently.

I don't think that one has to be a literary Sherlock Holmes to tell by reading the paper who wrote what. I mean, the styles are entirely different. One of them is a rather clipped, succinct style, and the other is a rather florid and — well, call it poetic if you wish, or hyperbolic or something — but at any rate, a diffuse style. And anyone who wants to, who is interested in literary Sherlock Holmesism, can find out just who wrote what by reading the article.

I wrote the pathology. Actually the study of the pathology was done mainly by Dr. Klemperer, Dr. Otani, and Dr. Oppenheimer. He [Oppenheimer] followed these things up in the lab, and he looked these things over, and they were again gone over by Dr. Klemperer and Dr. Otani, and some animal inoculations were made from titrated glands, etc. to see whether tuberculosis was present or not. And a considerable study was made to see whether we could ever find any evidence of caseation. We never found any evidence of caseation, although from many other standpoints, both in the local specimens and in the glands, there were things that looked very much like tubercles. But never in any instance was the tubercle bacillus found in smear or culture, and caseation was never demonstrated.

Getting Dr. Berg to participate in the paper was quite a job. There was one thing about Dr. Berg. He had a peculiar type of integrity about these things, and he would never permit his name on a paper if he didn't actually do the writing. I mean, it's a far cry from what we have today, where thousands at the bidding of the chief, post over land and ocean without cease, to get various arbeits [Editor's note: German for "jobs"] under way and to write them up, and then to have the chief's name, like Abu Ben Adam's, leading all the rest. But Dr. Berg, being an old-fashioned gentleman, brought up in the Victorian code of morals which we all rather snicker at nowadays, nevertheless would never permit his name to be put on any paper that he hadn't written. He just wouldn't have his name on it. We kept after him time and time again. And as a matter of fact, whenever I've ever had anything to say about the paper, I've always brought out the fact that actually, if it wasn't for Dr. Berg, who had the intestinal fortitude — and it took some in those days, in the 1920s, to do the massive resections that he did — certainly regional enteritis would not have come from this institution. (L. Ginzburg)

Footnote by Dr. Janowitz (1997):

Ginzburg told me that Dr. Berg insisted both that his own name should not be on the paper and that the three authors' names should be in alphabetical order.

In 1965 Dr. Winkelstein recalled (103):

I think that I know at first hand exactly what took place at the time of this so-called discovery of regional ileitis or regional enteritis.

What happened was this. Dr. Berg, A.A. Berg, was very interested in the findings, in his surgical material . . . which, as you know, was vast . . . something like six to eight operations a day, year in year out . . . finding inflammatory tumors in various parts of the gastrointestinal tract: stomach, small bowel, and in the colon. Dr. Berg was a very busy man, in private practice and surgically, operating all the time, and couldn't make these studies himself. So he assigned all these cases to two young men who at the time were adjuncts and attending surgeons in the

Hospital, Drs. Leon Ginzburg and Gordon Oppenheimer. And for a certain number of years, they collected these cases. They collected quite a few cases and they put them together in a paper. This paper was entitled "Non-Specific Granuloma of the Gastrointestinal Tract."

There were various headings for the different types of granulomas or inflammatory lesions of the gastrointestinal tract in this paper. This paper was written for presentation before the American Gastroenterological Association, I say this with all honesty and sincerity and clear recollection of what happened . . . before Dr. Crohn, Burrill Crohn, had ever heard of the disease called terminal ileitis. In this paper, I believe that Drs. Ginzburg and Oppenheimer had either fourteen or sixteen cases, [in] which they described both the clinical and the pathological characteristics of the disease, very correctly.

Some time after this paper was written, but before it was presented to the American Gastroenterological Association, a patient consulted me in my office. This patient had a bloody diarrhea, and he said, "It's due to hemorrhoids," and he wanted me to treat him. I said I refused to treat him unless I examined, with sigmoidoscopy and barium enemas and GI X-rays and so on. . . .

He went to Dr. Crohn's office. Dr. Crohn at once diagnosed tuberculosis of the intestine, and he sent him to Florida to bask in the sun. While there, he suddenly developed an intestinal obstruction and was rushed back to New York, and Dr. A.A. Berg operated on him. Dr. Berg believed in resection of the terminal ileum for terminal ileitis, as it was called then, or regional ileitis or enteritis, as we call it now. So he resected the involved area, and did either an ileotransverse colostomy or an ileosigmoid colostomy, I don't remember which.

Dr. Crohn's name was not on that paper, with one exception, which I'll tell you in a moment. Dr. Crohn came running to the pathology laboratory. At that time I was a volunteer assistant in pathology, and I had this specimen. I was studying it. Dr. Crohn was unable to come to the operation, but he wanted to see this specimen, since this boy had been his patient. I opened the specimen and showed it to him. He said, "What is this?" I said, "This is terminal ileitis." "What is terminal ileitis?" he said to me. "I never heard of it." So I explained to him: Drs. Ginzburg and Oppenheimer had sixteen cases from Dr. Berg's service. We know all about it . . . it's an inflammatory lesion, it's not tuberculosis, it's not a tumor, it's not a malignancy. And we didn't know the etiology, but it belonged in this group of the gastrointestinal tract.

So, as luck would have it, a few weeks later Dr. Crohn ran into a patient. He was the examining physician for some fraternal organization, and he sent in a patient to the ward that had the same lesions. To his credit, I must say that he got quite excited about this . . . not knowing anything about the disease before. It seems that he and Dr. Berg for a long time had been enemies. He had worked with Dr. Wilensky, and they both published some papers, or they rubbed Dr. Berg the wrong way, and he disliked both of them exceedingly. . . .

So Crohn went to Berg, and he told him he was very interested in this subject. Berg didn't care about Ginzburg and Oppenheimer, two young adjunct attending surgeons, and he gave them orders to turn over that part of the study to Dr. Crohn from that point on. They resisted this very strongly. And the Hospital . . . whether it was the board of directors or the Superintendent of the Hospital or the medical staff . . . appointed a committee to look into this. The committee reported that Dr. Berg and Dr. Crohn were 100 percent wrong, and that the disease belonged to Ginzburg and Oppenheimer, but in view of the fact that if this was brought out outside of the Hospital it would cause a lot of scandal, they decided to drop the whole matter, and let things take their natural course.

The course they took was that Dr. Berg threatened to get Dr. Ginzburg and Dr. Oppenheimer out of the Hospital if they didn't fall in with his wishes and turn that part of the study over to Dr. Crohn. And Dr. Crohn took it over from that point on, published the big paper with the other two in 1931 [1932]. Their paper had been written a couple of years before that, I believe. Dr. Crohn is a wonderful publicist, as a speaker and as a writer, and he quickly put this on the map, to the extent that it is now known as "Crohn's Disease," which is absolutely unfair. In the first place, it's not a new disease. In the second place, he was not the first to describe it, and he has never anywhere, publicly or in writing, said that the credit belongs originally to Dr. Berg, for separating this material, and after that to Ginzburg and Oppenheimer, who wrote the first description and collected the cases. (A. Winkelstein)

Fig. Drs. Oppenheimer, Crohn and Ginzburg

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19

Inflammatory Bowel Disease after 1932

Henry D. Janowitz, M.D.

Abstract

The clinical diseases of ulcerative colitis (UC) and Crohn's disease (CD) were defined by 1932–1933. After that, the major conceptual developments were the recognition that regional enteritis could clearly involve the colon, and that cancer and toxic megacolon could occur in both CD and UC. In the last half of the 20th century the main thrust of gastroenterology at The Mount Sinai Hospital has been in inflammatory bowel disease (IBD), with contributions to extra-intestinal manifestations, measurement of clinical activity in CD, the natural history of the placebo arm of controlled trials, complications and therapy with corticosteroids, 5-ASA, 6-mercaptopurine, immunomodulators and cyclosporine. Actuarial life tables were introduced for postoperative recurrence and re-operation rates, as well as for quality of life analysis. Two forms of CD were defined, perforating and non-perforating, and the role of the fecal stream was explored in light of the higher risk of recurrence after operations with anastomosis as compared with ileocolostomy. **Key Words:** Inflammatory bowel disease, regional enteritis, ulcerative colitis, Crohn's disease.

THE STUDY OF INFLAMMATORY BOWEL DISEASE (IBD) has a long history at The Mount Sinai Hospital. The preceding section by Hugh Baron documented the path that led to the discovery of the disease we now call Crohn's disease (CD). By 1932–1933, the papers of Ginzburg and Oppenheimer (presented before the American Gastroenterological Association), Crohn, Ginzburg and Oppenheimer (before the American Medical Association), and by Ginzburg and Oppenheimer (before the American Surgical Society) had described the entity not only in the ileum, but in the colon as well. With the subsequent description of cecal involvement (1) and the recognition of perineal disease (2), the basic clinical and pathologic features of this still enigmatic, serious, chronic and lifelong disorder were in place.

The 1930s to the 1950s

One would have expected an explosion of interest and study at the institution where it was discovered. Crohn continued to collect his series of cases, and with John Garlock, his surgeon, reported the results of resection (3, 4). In 1939, Ginzburg and his colleagues noted the surprising effects of bypassing the ileal lesion by diversion of the intestinal fecal stream (5). However, gastroenterologists at The Mount Sinai Hospital did not focus intensely on CD. This was especially so in the question of colonic involvement. Bargen and Weber (6) and Crohn and Berg (7), in the 1930s, called attention to "right-sided colitis," and several years later, in 1952, Wells (8) recognized "segmental colitis" as a variety of CD, separating it from ulcerative colitis (UC). Indeed, most American gastroenterologists remained indifferent as to this important feature of CD. This held true not only for Crohn himself but for the other gastroenterologists at Mount Sinai, except for Richard Marshak, the radiologist, who firmly maintained and lectured on the fact that regional enteritis could clearly involve the colon (9).

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Two factors were probably important in causing this delayed recognition of Crohn's colitis. First, the focus of clinicians such as Asher Winkelstein, and radiologists such as Bernard Wolf, was directed to peptic ulcer disease and hiatal hernia. The Gastrointestinal Research Laboratory, directed by Franklin Hollander and sponsored by the surgical departments at The Mount Sinai Hospital, especially that headed by Ralph Colp, was centered on ulcer disease, acid secretion, vagotomy, and the mucus barrier of the stomach (see Mt Sinai J Med 2000; 67:14–40). Additionally, David Dreiling had started his work on the pancreas in this laboratory (see Mt Sinai J Med 2000; 67:68–75).

Perhaps more important was the strong stand that the pathologist, Sadao Otani, had taken. He had insisted that the ileocecal valve separated regional ileitis from ulcerative colitis. It was the publication by Lockhart-Mummery and Morson (10) and the worldwide acceptance of their concept of CD of the colon that really opened the floodgate at this institution.

Some indication of the climate of opinion at Mount Sinai during this interval may be seen in the fact that, when I arrived as an intern in November 1939, seven years following the seminal papers, the general clinical attitude was tinged with slightly skeptical amusement at Crohn's interest in regional enteritis. When I returned again in 1950, after World War II and a period of research elsewhere, the climate had changed. Senior clinicians, and especially radiologists, were intensely interested in IBD. Marshak meticulously described the evolution of regional enteritis as it appeared in serial x-ray films during the life of a patient (11).

Interest too was centered on ulcerative colitis, focused, in particular, on toxic dilation of the colon. R.H. Marshak, L.J. Lester, and A.I. Friedman (12) had described the megacolon of ulcerative colitis and coined the term "toxic megacolon" and Greenstein et al. (13) followed up with a study of the outcome of toxic dilation of the colon in UC and CD. Even the problem of cancer in inflammatory bowel disease had been recognized. Crohn had described the first case of cancer of the colon in UC in 1925 (14). In 1956, Ginzburg et al. (15), described the first case of carcinoma (of the jejunum) in regional enteritis.

From the 1960s

The formal organization of gastroenterology at The Mount Sinai Hospital in 1958, with the founding of the first separate division within the Department of Medicine, marked the beginning of more intense interest in many aspects of inflammatory bowel disease. Contributions by those in Surgery, Radiology and Immunology are detailed in this issue, by Aufses, Maklansky and Mayer. By the end of the 1960s, an informal group of clinical investigators was slowly forming. Present, Korelitz, and myself, from the Division of Gastroenterology, were later joined by Sachar and Meyers. The combined cooperation of the surgeons Aufses, Gelernt, and Greenstein played an important part. Greenstein had begun to assemble a database of all patients with IBD (UC and CD) seen at the hospital, making an especially important contribution. The return of Lloyd Mayer to The Mount Sinai Hospital, after a brilliant stint at the Rockefeller Institute in the laboratory of Henry Kunkel, further strengthened the collaborative team in immunology, while a younger generation of graduating fellows who became involved with this group included Lichtiger and Kornbluth. These contributions are now reviewed.

The Natural History and Complications of IBD

The first American paper on Crohn's colitis in the post-Lockhart-Mummery and Morson era appeared in *The New England Journal of Medicine* in 1963, a joint paper of Lindner (a fellow in Gastroenterology), Marshak, Wolf (Radiology), and myself (16). Articles on "granulomatous colitis," the term we used at The Mount Sinai Hospital to avoid offending Leon Ginzburg, appeared in *JAMA* in 1965 (17). Others were then published in rapid succession in the *Annual Review of Medicine* of 1966 on ileocolitis (18) and in *Gut* in 1966, with Marshak as a co-author (19).

Extra-intestinal Manifestations of IBD

The long-standing interest in these manifestations culminated in 1976 in the paper most frequently cited in the literature, which was from this division (20). It offered for the first time a classification into the categories of "colitis associated," "results of small bowel pathology," and "an immunological group." This classification helped sort out the protean manifestations associated with inflammatory disease activity (especially in the colon) from those unrelated to disease activity.

Measurement of Clinical Activity in CD

The measurement and quantification of disease activity in CD represent a continuing problem. A wide range of laboratory tests, including labeled colonic or fecal leukocytes, are widely used by different clinical investigators. Following the report of Thomas et al. (21) on the use of random stool specimen concentrations of fecal α-1-antitrypsin in children with CD, we reported that this technique was a useful measure of clinical activity of CD in ileum and colon in adults (22) and the effects of therapy and anatomical extremes in this disorder (23). Other studies indicated that the erythrocyte sedimentation rate (ESR) was also a useful indicator of disease activity, but primarily in extensive colonic disease as opposed to small bowel involvement (24, 25).

Natural History of Inflammatory Bowel Disease

More recently, our interest in the natural history of IBD led to the novel suggestion that we look at the "placebo arm" of published trials. Since almost all patients described in the literature with these diseases have been treated with a variety of drugs, we used the placebo arm of controlled trials as a measure of the natural history of CD and UC. This approach, focused on the placebo response in IBD both in Crohn's disease (26) and ulcerative colitis (27), has markedly affected evaluations of results of current therapeutic trends.

Complications of Inflammatory Bowel Disease

The complications of IBD have been explored with an avid and active interest on the part of the division of gastroenterology.

Cancer in IBD

Cancer in IBD is fully discussed by Adrian Greenstein (see this issue). Here we call attention to the early recognition of cancer risk in Crohn's disease, not only in bypassed loops (28, 29), but also in long-standing Crohn's disease of unoperated small bowel and colon (30–33).

Toxic Dilation of the Colon

An early interest in toxic dilation of the colon was sparked by Marshak (34), and again in 1985, in a paper by Greenstein, Sachar and others (13), devoted to the outcome of toxic dilation in patients with these diseases. In 1980, pneumomediastinum was described as a perforating complication of toxic dilation (35) and in 1988 Present reported on his therapeutic use of "rolling" of the patients with toxic megacolon (36).

Obstructing Hydronephrosis

The discussion of renal disease in IBD began at The Mount Sinai Hospital with the report by Deren, Porush, Levitt and Khilnani on the study of kidney stones as a complication of UC and CD (37). The important and, up to then, frequently unrecognized obstructive hydronephrosis complication of Crohn's disease was detailed by Present, Rabinowitz, Banks and Janowitz (38).

Suppurative pylephlebitis with liver abscess was recorded early in 1962 (39).

Blood Disorders

Autoimmune hemolytic anemia was described in some detail along with an analysis and evaluation of its current therapy in 1979 (40). Cryoglobulinemia with skin involvement, including gangrene of fingers and toes, was described early in 1979 and in 1981 (41, 42). The association of acute myelogenous leukemia with ulcerative colitis was first correlated by Fabry, Janowitz and Sachar with the considerable amount of previous x-ray exposure in these patients (43). Additional reports from other institutions then followed.

Pyoderma Gangrenosum

Pyoderma and trauma to the upper extremities were reported in 1981 as being associated with IBD, their existence having been known to dermatologists but apparently not recognized by gastroenterologists (44). An important study of the outcome in patients with pyoderma treated by colectomy appeared in 1983 (45). It showed that patients with active colitis healed promptly, while patients with less active disease required up to one year to heal, although all did heal eventually.

Amyloid

Amyloidosis, especially renal amyloidosis, has been of continued interest to the division. One of the earliest series (five cases of amyloidosis) in regional enteritis was published in 1960 (46) and the 50-year experience with 25 patients was recently brought up to date in *Medicine* (47) in 1992. The first cases of renal amyloidosis with severe proteinuria associated with inflammatory disease treated successfully with colchicine were reported by Meyers, Janowitz, Gumaste and other colleagues (48).

“Metastatic” CD

Along with cutaneous manifestations of CD patients, an early interest in “metastatic” CD was reported from the gastroenterology division and the Department of Dermatology in 1984 (49).

Pancreatitis

A very early report by Meyers and colleagues from the division stressed the curious association of acute pancreatitis with active Crohn’s disease (50). This may be related to the recent report of elevated titers of pancreatic tissue antibodies in Crohn’s disease (51).

Central Nervous System Involvement

Early on, Silverstein and Present called attention to the tragic situation of central nervous system catastrophes, in the form of cerebrovascular occlusion, in some young patients with CD (52).

Pregnancy and IBD

Mount Sinai gastroenterologists have had a very long and active interest in the effects of pregnancy on the course of IBD patients and on the outcome of the fetus, beginning with the early paper of Crohn, Yarnis and Korelitz (53). Korelitz has continued to review his and his colleagues’ experiences in this area, reporting his data from time to time. His review on the effects of sulfasalazine and steroids on pregnancy and the fetus has given important reassurance to gastroenterologists worldwide of these drugs’ safety (54). Present and co-workers will soon report on the largest series of pregnant women who have conceived successfully while on 6-mercaptopurine; this will help resolve the question of its safety.

Therapeutic Contributions

The division has made important contributions to the medical therapy in IBD in several areas.

ACTH versus Hydrocortisone

The introduction of steroid therapy in 1954 by Truelove and Witts (55) focused clinical attention for a long time on the intravenous administration of ACTH and the use of steroids and the routes by which they were administered. The publication by Meyers, Sachar, Goldberg and Janowitz (56), comparing the clinical responses to intravenous ACTH and hydrocortisone of patients sick with ulcerative colitis, showed that the response depended on patients’ recent experiences with steroids. ACTH was superior to hydrocortisone for patients who had no recent exposure to prednisone. Resisted at first, the concept seems now generally accepted for ulcerative colitis.

Mesalamine

An early paper by Meyers, Sachar and Janowitz, joined by Present (57), showed the efficacy of olsalazine (Dipentum) in ulcerative colitis in a prospective, randomized, double-blind, dose-ranging, placebo-controlled trial. This study helped to establish this variant of 5-ASA for patients allergic to or intolerant of sulphasalazine (Azulfidine).

Immunomodulators

Although azathioprine had been used since 1964 for the treatment of UC, fear of malignancy and “cure” by colectomy, with a reasonably normal lifestyle with the Brooke ileostomy had led to its disappearance from the therapeutic armamentarium for chronic ulcerative colitis. There can be no doubt that the introduction of 6-mercaptopurine by Present, Korelitz, Wisch, Glass, Sachar, and Pasternack for the treatment of Crohn’s disease in a long-term, randomized, double-blind study (58) marked an important turning point in the history of treatment for CD. The detailed story of the slow reception, published controversy and ultimate acceptance of this form of therapy (59) is given by Korelitz and Present (see this issue). Its triumphant story is to be attributed to the persistence and determination of the investigators, and their careful follow-up study on toxicity and malignant potential. Its worldwide acceptance is a feather in the cap of this division.

Cyclosporine

Although cyclosporine has not proved to be very effective in CD, its introduction for severe ulcerative colitis refractory to steroid therapy by Lichtiger, Present, Kornbluth and co-workers in 1994 signaled another important new modality for these seriously ill patients facing urgent colectomy (60). Careful follow-up studies of Kornbluth and others on toxicity and quality of the long-term results have already furnished us with valuable information on its long-term benefits and risks (61, 62).

Omega 3 Fatty Acids

Although the real place of fish oil omega 3 fatty acids as an anti-inflammatory agent and as a treatment in UC and CD is yet to be defined, interest in this modality was shown by a very early open trial for UC in this division (63).

Mount Sinai Gastroenterology and Its Interaction with Patients

At present, with our intense interest in the effects of IBD and its therapy on the lives of our patients, it is important to remember Mount Sinai's contributions which go back a long time. One of the earliest papers on the "quality of life" with IBD was a publication on the study of the quality of life after surgery for CD in the form of psychosocial assessment, published twenty years ago (64). More recently, direct comparisons are being made between medical and surgical treatment, for their quality of life outcomes (65).

The formation of the National Foundation for Ileitis and Colitis (NFIC), now known as the Crohn's and Colitis Foundation of America (CCFA), at The Mount Sinai Hospital, was an important step in organizing the partnership of the scientific community with the lay public, especially the families of patients with IBD 33 years ago. Present was its first Research Fellow, and was succeeded by Sachar. Its National Scientific Advisory Committee was chaired first by Janowitz (1969 – 1979) and later by a Mount Sinai alumnus, Lenox Hill's Korelitz (1981 – 1984). This partnership now raises millions of dollars for research, patient information books (edited by Present and colleagues) and physician education, an amount far greater than the NIH budget for IBD.

The Ileostomy Society, organized at Mount Sinai by Dr. Albert Lyons, was really the first self-help organization for the sufferers of IBD.

Conceptual Contributions

There are four areas in which gastroenterology at Mount Sinai has made significant contributions to conceptual advances in IBD. The first was the use of actuarial life tables for postoperative recurrence and re-operation rates in IBD. The paper by Greenstein, Sachar, Pasternack and Janowitz (66), which compared crude and cumulative rates, was among the first such uses of the life tables as a statistical method in IBD. No publication on the long-term follow-up in this field can now be accepted without the use of this method of presentation.

Second, since studies of the natural history of untreated IBD patients have not been done, and cannot be done, the use of the placebo arm of controlled trials as introduced by Meyer and Janowitz, when applied to Crohn's disease (26) and UC (27), revived interest in the placebo effect in IBD.

Third, based on Greenstein and Sachar's concept, the recognition of two clinical forms of CD, a perforating and a non-perforating one, and their indications for repeated operation as published in *Gut* (67), has attracted considerable attention and recent confirmation. This concept has proved central to current classifications of patients with Crohn's disease (68).

Fourth, workers in the division have recently questioned how effective our current drugs are in the treatment of CD (69), UC (70) and severe Crohn's and ulcerative colitis (71). The first two papers used the method of meta-analysis, and the third was an analytic review of selected clinical trials. The thrust of these papers is to point out the relatively limited effectiveness of our traditional and current drug therapies.

The Role of the Fecal Stream in Crohn's Disease

Leon Ginzburg and his colleagues, Ralph Colp and Marcy Sussman (5), noted that in patients with CD, diversion of the intestinal stream led often to such clinical improvement of the primary lesion in the cecum and/or ileum that the intended 2nd stage resecting the central lesion could be "indefinitely postponed." The important observation stimulated a long-standing interest in the division on the role of the fecal stream on the pathogenesis of localized CD.

Further evidence slowly has accumulated that surgery with anastomosis is associated with a higher risk of recurrence than ileocolostomy. Emphasized by De Dombal, Goligher and colleagues (72, 73), similar findings were also pointed out by Sachar and his colleagues at The Mount Sinai Hospital (74, 75). We have confirmed this again in a new study of end ileostomy in CD (76).

As a result of these lines of evidence, we (Janowitz, Croen, Sachar) have prepared a comprehensive historical and analytic review of all the clinical and laboratory evidence in this area (77). Many, but not all, of the accepted clinical features of CD are consistent with the contributory role for the intestinal stream concept, and fit in with recent animal studies on the role of luminal bacteria in inducing ileal and colonic inflammatory changes in some spontaneous, or transgenic, or "knock-out species."

Interaction with the Official World of IBD Activity

Gastroenterologists at The Mount Sinai Hospital have played important roles as presidents of the American Gastroenterological Association (Crohn 1935, Janowitz 1972); as the chairman of the International Organization for the Study of IBD (Sachar 1989 – 1992); and in founding the new series, the *American Journal of Digestive Diseases* (Janowitz, 1968 – 1978). Sachar launched the AGA's clinical teaching project with its first unit on IBD (78), and has contributed a number of influential and lively editorials to *Annals of Internal Medicine, Digestive Diseases and Sciences, Gastroenterology, Gut, Journal of Clinical Gastroenterology,* and *The New England Journal of Medicine.*

Monographs from the division include those of Waye on endoscopy (79), Janowitz on a clinical approach to IBD (80), and G.E. Friedman on therapeutic pharmacology in gastroenterology (81), a book by Marshak and Lindner (82), and patient information books by Present and colleagues (83, 84). The place of The Mount Sinai Hospital in the clinical world of management of IBD was advanced significantly by the endoscopic techniques used by Jerome Waye. He was the first to perform colonic endoscopy without radiographic control, and has published, lectured and edited books on gastroenterological endoscopy. Members of the original gastroenterological group in IBD played a significant role in the evolving status of the American College of Gastroenterology. The following have been among its presidents: David Dreiling, Jerome Waye, Burton Korelitz, Arthur Aufses, and Lawrence Brandt.

Appendix

The Contribution of the Division of Gastroenterology to Academia: Former Fellows and Members of the GI Division since 1958

Name	Position
J. Hugh Baron	Former President, British Society of Gastroenterology; Consultant at Hammersmith and St. Mary's Hospitals, Imperial College School of Medicine, London
Alvin Gelb	Chief of Gastroenterology Division, Beth Israel Hospital, New York
Peter Banks	Clinical Director of Gastroenterology, Brigham and Women's Hospital, Boston, MA
Fred Saibil	Head of Gastroenterology, Sunny Brook Health Science Center, Toronto
Lawrence Brandt	Chief of Gastroenterology, Montefiore Medical Center, The Bronx
Jane Geders	Chief of Gastroenterology and Hepatology, Methodist Hospital, Brooklyn
Mark Korsten	Gastroenterology Fellowship Program Director and Associate Chief of Medicine, Bronx VA Medical Center
Vivek Gumaste	Chief of Gastroenterology, The Mount Sinai Service of the City Hospital Center at Elmhurst, Queens

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The History of Surgery for Crohn's Disease at The Mount Sinai Hospital

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Abstract

Almost certainly, the physicians and surgeons of The Mount Sinai Hospital cared for patients with inflammatory bowel disease prior to 1932. However, the accepted beginning of the surgery of granulomatous inflammatory bowel disease (IBD) and Crohn's disease (CD) at our institution occurred when the landmark paper by Crohn, Ginzburg, and Oppenheimer was published in 1932.

As a major referral center for patients with both medical and surgical complications of IBD, the surgical service has had a long and abiding interest in the disease. This review highlights the major contributions of our staff to the management of this illness over the past 67 years.

Despite major innovations in both medical and surgical management of patients with Crohn's disease, individuals suffering from this condition are ideally managed by a multidisciplinary team. **Key Words:** Crohn's disease, surgery.

June 8, 1855 — THE DOORS of The Jews Hospital opened to admit patients. Patient No. 1 was Mr. L.S., a forty-two-year-old white male with a fistula-in-ano. He was operated on by Dr. Israel Moses, one of the three attending surgeons on the staff at that time. The operation was successful and the patient was discharged on June 14th (1). Seventy-seven years later, Crohn, Ginzburg, and Oppenheimer (2) noted that the disease they were reporting was "associated with the formation of multiple fistulas," and in 1934, Bissel (3) provided the first report of a perianal fistula in association with ileitis.

Did Mr. L.S. have Crohn's disease?

April 17, 1866 — The name of our institution was changed to The Mount Sinai Hospital.

April 14, 1889 — Dr. John Wyeth, who joined the surgical staff in 1880, operated on a 12-year-old male with abdominal pain of four days' duration and drained a large abscess. Postoperatively the patient developed an enterovesical fistula which closed slowly (4). Although this young patient had had no prior history, and the history of the present illness was most suggestive of appendicitis, the development of an enterovesical fistula was certainly not in keeping with the diagnosis of appendicitis, but is a significant complication of Crohn's disease.

Did this patient have Crohn's disease?

December 30, 1899 — Dr. Howard Lilienthal (5) operated on a 21-year-old female who "had for years suffered from diarrhea, accompanied by hemorrhages and the passage of foul mucus, and finally become so weak and anemic that a left inguinal colostomy had to be performed to give rest to the lower portion of the colon and rectum. The surgeon who opened the colon at this time saw that the walls of the viscus were covered with polypoid growths which bled easily even on gentle manipulation. The patient was very much benefitted by the operation, the hemorrhages finally ceasing so that it was thought best to close the opening. No sooner had she left the hospital, however, than her old trouble returned in all its severity. . . . Dr. Lilienthal first performed a cecostomy for irrigation of the colon, then on March 6, 1900 performed an ileo-sigmoid anasto-

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mosis (using a Murphy button to perform the anastomosis) with exclusion of the terminal ileum and the remaining colon. Three months later, the excluded bowel was removed. After two more procedures, the patient did well and on January 14, 1901 was presented to the New York Surgical Society as a case of 'hyperplastic colitis.' At that time the patient was 'in excellent general health and has 2 movements a day. . . ." (6)

Did this patient have Crohn's disease?

February 18, 1919 — Dr. A.O. Wilensky (7) operated on a twenty-three-year-old male with a right lower quadrant mass. The past history included diarrhea of about two years' duration, weight loss and anemia, and an attack of acute suppurative appendicitis treated by appendectomy. Six months after the procedure, he developed pain in the right lower quadrant and a mass appeared. The mass was in the cecum and was resected with anastomosis. Although a postoperative fecal fistula necessitated another operation, the patient did well save for episodic diarrhea, until December 1920, when an episode of acute intestinal obstruction required a resection of about twelve inches of the ileum. He again did well for about two years, when he developed an episode of peritonitis, for which no cause was found at laparotomy. Following drainage, he recovered. Pathological study revealed a granulomatous lesion of the cecum with multiple giant cells, usually present within clumps of lymphocytes. "The entire thickness of the gut appears densely infiltrated. . . . A rather strange finding is the presence of giant cells in what seems an apparently normal lymph follicle in a portion of the contiguous colon that is otherwise entirely normal." Examination of the small bowel revealed that "the gut is extremely thickened and enlarged. The peritoneal surface is much congested and is covered with fresh fibrin. Cross-section shows an immense thickening of all the coats of the gut so that the lumen is merely a bare slit. The infiltration involves the adjacent mesentery which averages 1 cm. In thickness . . . fresh fibrin covers the surface of the mucosa. Removal of the fibrin reveals numerous superficial ulcerations." Microscopic examination was similar to the colon, but there were far more giant cells, the majority of which contained an unrecognizable foreign body.

Did this patient have Crohn's disease?

May 13, 1932 — Dr. Burrill B. Crohn, as the sole author, presented a paper entitled "Terminal Ileitis" at the annual meeting of the American Medical Association in New Orleans. In the discussion that followed, Bargen stated that "several cases of this type have come to operation annually at the Mayo Clinic." He felt that the term "terminal ileitis" was inappropriate because the disease was not a "terminal illness," and he also prophesied that the disease would be described elsewhere in the intestinal tract. Crohn's manuscript was published in the *Journal of the American Medical Association* (2) in October 1932, and the name of the syndrome was changed to "regional ileitis." Also, the names of Drs. Leon Ginzburg and Gordon S. Oppenheimer were added as co-authors, since they had accumulated a large series of cases, not otherwise categorized, of unusual conditions of the terminal ileum, which included the cases presented by Crohn. Their work was presented (also in May 1932) at the meeting of the American Gastroenterological Association and finally published in the *Annals of Surgery* (8) in January 1933. At the time, Dr. Oppenheimer, who subsequently became the Chief of Urology at The Mount Sinai Hospital, was working in the pathology laboratory and Dr. Ginzburg was the assistant to Dr. A.A. Berg, the surgeon who had operated on the 14 patients in the original series.

Although the patients described earlier may or may not have had Crohn's disease, there is little doubt that the disease had existed prior to 1932. But was it a new disease? Janowitz (9) speculated that "one cannot escape the conviction that this really is a new disease, which emerged in the early part of the century, for it is difficult to believe that the great European pathologists of the 19th century who did such careful autopsies would have missed the striking pathologic entity or confused it with tuberculosis, whose appearance they knew so well." On the other hand, cases reported more than one hundred years earlier are most suggestive, and the cases reported by Dalziel (10) in 1913 almost certainly had granulomatous disease of the bowel, affecting both small and large intestine. Six of nine were successfully operated on.

The accepted beginning of the surgery of granulomatous inflammatory bowel disease (IBD) and Crohn's disease (CD) at The Mount Sinai Hospital occurred when the landmark paper by Crohn, Ginzburg, and Oppenheimer was published in 1933 (2). The fourteen patients who made up this series of cases were all operated on by Dr. A.A. Berg, one of the leading surgeons of his day and a chief of service at The Mount Sinai Hospital. Dr. Ginzburg stated (11): "Dr. Berg was an extraordinary individual. The extent of his surgical practice was almost incredible in its day, and it would be difficult for one to believe at present. He operated both morning and afternoon six days a week, and not infrequently on Sunday as well." Berg, as the surgeon for all of the patients, was given the opportunity to be a co-author. However, he declined (12), since it was his policy not to put his name on a paper unless he had personally written a significant portion of the manuscript. Had he accepted, and since the authors were listed alphabetically, we might now be talking about "Berg's disease" (see Baron article, this issue).

In 1934, the first report of a patient with ileitis crossing the ileocecal valve to involve the cecum and ascending colon was reported by Dr. Ralph Colp (13). Dr. Colp was a graduate of the College of Physicians and Surgeons of Columbia University, trained at the Presbyterian Hospital, and was a senior surgeon at the Beekman-Downtown Hospital before he joined the staff of the Department of Surgery of The Mount Sinai Hospital in 1923. The patient, a twenty-two-year-old medical student, had been operated on at the Beth Israel Hospital where Dr. Colp was a consultant. Dr. Colp noted that "the microscopical pathology of both the ileum and the cecum were similar, that of a nonspecific granuloma." He went on to say that "nonspecific granulomas of the terminal ileum, the ileocecal region and the colon are probably one and the same disease." Although Hirschman of Detroit, in his discussion of Crohn's presentation, had cited the case of an 18-year-old male with "chronic ulcerative colitis" of 9 years' duration, who at operation was found to have a "large doughy thickened ileum" of about 12 inches in length, Colp's report is the first documented and published case of granulomatous ileocolitis.

The years between 1932 and 1960 were punctuated by tremendous advances in our understanding of this newly described entity. Numerous reports documented that granulomatous inflammatory bowel disease was truly panenteric, and the distinction between granulomatous and ulcerative colitis was firmly established by Lockhart-Mummery and Morson (14) in 1960. Until that time (and even after, in some quarters), granulomatous colitis had been considered to be a variant of ulcerative colitis. What in retrospect was clearly granulomatous ileocolitis had then been considered by most gastroenterologists and surgeons to be ulcerative colitis or a variant thereof, in association with regional or granulomatous disease of the small bowel.

It must be remembered that, in the years that these early patients were operated on (1925–1935), antibiotics were nonexistent, fluid and electrolyte management was in its infancy, and blood transfusions were a tour de force. As a result, one-stage ileocolic resection, the preferred operation today and the operation performed by Berg and others of his day, then had a significant mortality rate, as high as 25%. As a consequence, many surgeons performed the procedure in two stages. In the first procedure, the ileum proximal to the diseased segment was divided, the distal end closed and the neoterminal ileum anastomosed to either the transverse or sigmoid colon. At a later date, the excluded segment was resected.

Two years after Colp's 1934 report, Berg (15), who had performed primary resections on all of the early cases, reported on "an operative procedure for right-sided ulcerative colitis." This was an ileo-sigmoidostomy with exclusion of the most distal ileum. In addition, however, the sigmoid proximal to the ileal anastomosis was divided, and the distal end closed. A stoma was created with the proximal end. This effectively isolated the colon, and allowed for drainage of colonic mucus and for irrigation of the colon via the stoma. Not all of these patients did well and several, therefore, had resection of the excluded bowel. The article (15) contains an artist's rendition of the specimens. One of them depicts a terminal ileum and colon with deep punched-out ulcers and significant thickening of the affected areas, almost certainly granulomatous disease rather than ulcerative colitis.

In 1938, Richard Lewisohn (16), best known as the individual responsible for the development of citrate solution for blood preservation, summarized the then current thinking of The Mount Sinai Hospital surgical staff. His conclusions are worth noting, as many are still relevant today:

> 1) Segmental or regional enteritis is not a rare disease. 2) Opinions differ widely not only as to the pathogenesis of these interesting lesions, but also as to the best method of surgical treatment. 3) The lesion is encountered most frequently in the terminal ileum. However, it may occur in any part of the gastro-intestinal tract. 4) It is doubtful whether segmental colitis and ileocolitis are clinical entities. They may represent an attenuated form of acute ulcerative colitis and ileitis. 5) Perianal fistulas are frequently encountered. 6) Ileocolostomy with division of the ileum may effect a complete cure. 7) In the presence of fistulous communications with other parts of the intestinal tract primary resection becomes mandatory.

Ileotransverse colostomy with exclusion became the procedure of choice at Mount Sinai, and in 1939 Ginzburg, Colp, and Sussman (17) presented 32 cases of "ileostomy with exclusion," at the meeting of the American Surgical Association. Nineteen of the procedures were performed as definitive surgery for inflammatory disease, and in 13 patients the operation was performed as a first-stage procedure in the management of carcinoma of the right or transverse colon. The development of this procedure was later eloquently described by Ginzburg in 1955 (18):

> Originally, localized ileitis was treated by ileocolic resection. Before the present era of antibiotics, blood banks, intestinal intubation and improved anesthesia, this procedure was accompanied by a mortality rate rarely under twenty per cent and at times considerably greater. In order to reduce the mortality, recourse was had to a two stage operation, the primary one consisting of an ileocolostomy with exclusion. Secondary operation revealed that recession of the active inflammatory process was present in the excluded loop in almost all cases. The routine second stage procedure was therefore abandoned and performed only on those few occasions where there was evidence that healing had not taken place in the excluded loop. The results following ileocolostomy with exclusion proved to be as good as that obtained following resection and were achieved with a negligible mortality.

This operation became known as "The Mount Sinai Operation." That it was a wise decision at the time was evident in the 1945 report by Garlock and Crohn (19) reporting the series of patients personally operated on by Dr. Garlock. For these 145 patients, the mortality rate was 16% for a one-stage resection (9/55), 12% (3/25) for a two-stage resection, and 0% in 65 patients treated with ileotransverse colostomy with exclusion. In 1980, 35 years later, we were able to report 100 consecutive ileocolic resections for CD without mortality (20). Today almost all major medical centers report large series of one-stage resection with minimal mortality. Unquestionably, the advances noted by Ginzburg have had a great impact on the improved results.

Ileotransverse colostomy with exclusion as a definitive procedure fell into disfavor when it became apparent that the procedure had deficiencies. The inflammatory process in the excluded loop did not always subside, and the right colon was unnecessarily sacrificed, thereby losing its water-absorbing capacity. The report of Greenstein and his colleagues (21), showing that the excluded loop was a major risk for the development of small bowel cancer, was probably the final nail in the coffin for this procedure. On the other hand, there will always be a role for this procedure in the rare instance of massive inflammatory reaction, where the surgeon feels that resection may prove fatal. In this situation, ileocolostomy with exclusion as the preliminary step in a staged procedure may prove to be lifesaving.

In the 66 years (1932–1998) since the first description of Crohn's disease, the surgeons and surgical specialists of the staff of Mount Sinai have contributed significantly to present-day understanding of the state of the art management of the disease and its complications. As The Mount Sinai Hospital has been a major referral center for IBD, its surgeons have amassed a broad experience in the management of the surgical issues confronting this group of patients and have shared their experiences via literally hundreds of papers. In the past thirty years, approximately 5000 patients with Crohn's disease and ulcerative colitis have been treated. In 1968, Dr. Allan Kark, the then chairman of the Department of Surgery, recruited Dr. Adrian Greenstein to the staff. Dr. Greenstein became the "keeper of the records"of our inflammatory bowel disease population. His publications on the extraintestinal manifestations of IBD (22) and the nature and magnitude of reoperation and recurrence (23), written in collaboration with our colleagues in Gastroenterology, are classics. His bibliography of more than 135 papers, 30 book chapters and innumerable abstracts has catalogued the gamut of IBD.

For more than twenty years, the Department of Surgery has encouraged medical students to participate in research. There have also been a number of outstanding fellows. Many of the surgical faculty have an uncanny knack of stimulating and encouraging the students and fellows to be academically productive. Utilizing electron microscopic techniques, Michael Marin, then a student and now a member of the faculty in vascular surgery, made significant contributions to our understanding of the earliest pathological abnormalities in CD (24–26). Anthony Pucillo did yeoman work on the papers relating to the development of cancer in bypassed loops (21) and was a co-author of papers on cancer in ulcerative colitis (27, 28). Among the fellows, Yamazaki and Ribeiro deserve special recognition for their contributions to the papers dealing with carcinoma of the small bowel in CD (29), the management of intra-abdominal abscess in CD (30), and a review of colorectal strictures in CD (31). One of Adrian Greenstein's many contributions related to the concept of two types of CD, i.e., obstructive and fistulizing (32). Originally criticized by many in the field, this concept is now generally accepted. Recent laboratory work by Dr. Robert Greenstein and colleagues (33) may provide the molecular basis underlying the concept.

Almost all of the abdominal surgeons in the department have contributed their knowledge and specific expertise in papers, monographs, book chapters, and reviews. Dr. Tomas Heimann has focused his efforts on the immunological aspects of CD, and their effect on the postoperative course and recurrence (34–40). His paper on the factors responsible for early symptomatic recurrence (41) was presented at the 1993 meeting of the American Surgical Association. Dr. Paul Tartter, one of the first to document the effects of blood transfusion on the immune system, has studied the effects of transfusion in CD patients undergoing surgery (42, 43). Dr. Isidore Kreel has had extensive surgical experience in the management of CD. In association with Dr. Arthur Aufses and then Dr. Gary Slater, he was one of the first to point out the value of ileostomy in CD (44, 45). Slater and Aufses have also been major contributors to what has been an important cooperative venture on the part of all of the surgeons of the department. A partial listing of other papers appears in the reference list (20, 46–66).

Mount Sinai Medical Center was one of the first academic medical centers to create a separate division of endoscopic surgery (1992) to promote the use of these new surgical techniques. The experiences of these laparoscopists with respect to resection for CD were reported shortly thereafter (67–69).

In conclusion, starting from the first description of the disease now known throughout the world as Crohn's disease, the surgeons of The Mount Sinai Medical Center have worked in close collaboration with colleagues in gastroenterology to the benefit of many grateful patients. This collaboration will continue to promote not only superior patient care, but also the future training of physicians and other health care workers in the ever-changing aspects of the treatment of Crohn's disease.

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Pioneer Gastroenterological Radiology Studies

Daniel Maklansky, M.D.

Abstract

In the middle third of the 20th century, Mount Sinai radiologists were able to describe and establish specific radiologic criteria for the diagnosis of many gastrointestinal diseases. They then delineated specific radiologic patterns to diagnose such diverse conditions as inflammatory bowel disease of the small bowel and colon, protein-losing disorders, vascular disease of the small bowel, benign and malignant tumors, metastases and lymphoma of the gastrointestinal tract. Richard H. Marshak, Bernard S. Wolf, and Mansho T. Khilnani were the leaders in these radiologic investigations which established criteria that enabled generations of subsequent radiologists to arrive at definitive diagnoses.
Key Words: Small bowel radiology, regional enteritis, Crohn's colitis, inflammatory bowel disease, diverticulitis, esophagus.

Introduction

Stimulated by the abundance of clinical material provided by the gastroenterologists on the staff of The Mount Sinai Hospital from the 1930s through the 1960s, Mount Sinai radiologists were able to collect, catalog, correlate and establish specific radiologic criteria for the diagnoses of a number of gastroenterological diseases and conditions, so as to enable generations of subsequent radiologists and gastroenterologists to arrive at definitive diagnoses.

Regional Enteritis

Once "regional enteritis" (Crohn's disease) had been described by Crohn, Ginsburg and Oppenheimer (1) and was generally accepted as a disease, many patients came to Mount Sinai's GI Clinic for treatment. And many came specifically to see Dr. Crohn himself, at his private office. In 1944, Dr. Richard H. Marshak joined Dr. Crohn's practice as his radiologist, at 1075 Park Avenue, New York, and had the opportunity to perform appropriate barium examinations on many patients with ileitis and other gastroenterological diseases. Within a few years, in collaboration with Dr. Bernard Wolf, Director of Radiology at The Mount Sinai Hospital, and Dr. Mansho Khilnani, Dr. Marshak was able to use this abundant material to identify the radiologic features of regional enteritis and present these findings in a logical and sequential fashion. Using this radiographic material, Dr. Crohn wrote a seminal monograph in 1949 (2), illustrated by Dr. Marshak's small bowel barium studies (Figs. 1–3), describing the pattern of radiologic changes in regional enteritis.

In 1953, Marshak and Wolf (3, 4) studied 71 cases of chronic ulcerative granulomatous jejunitis and explained the sequence from the nonstenotic to the stenotic phase. Furthermore, they demonstrated the diffuse nature of jejunoileitis which sometimes could involve the entire small bowel. They presented criteria to distinguish the marked thickening and nodularity of the folds associated with Crohn's disease from similar findings in other entities, such as lymphoma.

Subsequently, Drs. Marshak, Wolf and Khilnani transformed radiology of the small bowel from the nonspecific diagnosis of "disordered motor pattern," so commonly offered in the 1940s and early 1950s, into a coherent understanding of the radiologic manifestations of a variety of small bowel diseases, including not

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Footnote: Figures 1–6 are illustrations of the original radiographs from the files and film library of the late Dr. Richard H. Marshak.

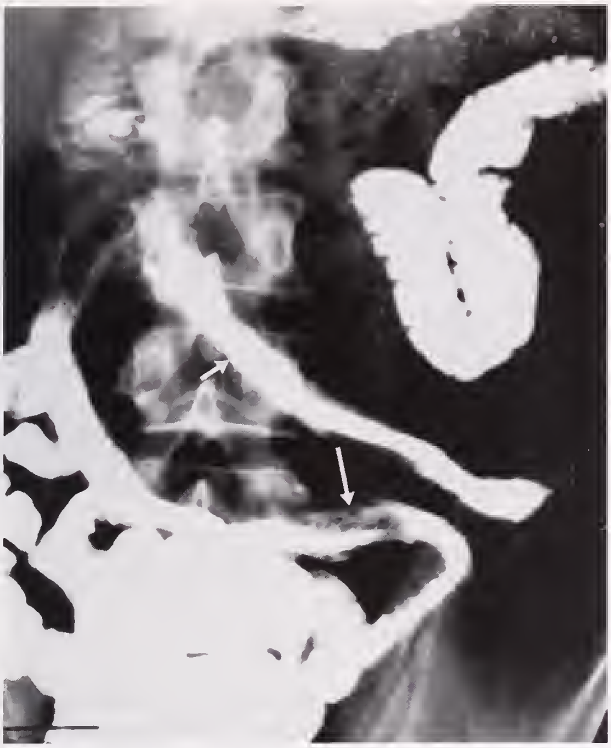

Fig. 1. Non-stenotic type of ileojejunitis. The loops are rigid and markedly separated. The mucosal pattern is cast-like (short arrow). Several pseudopolyps are also identified (long arrow).

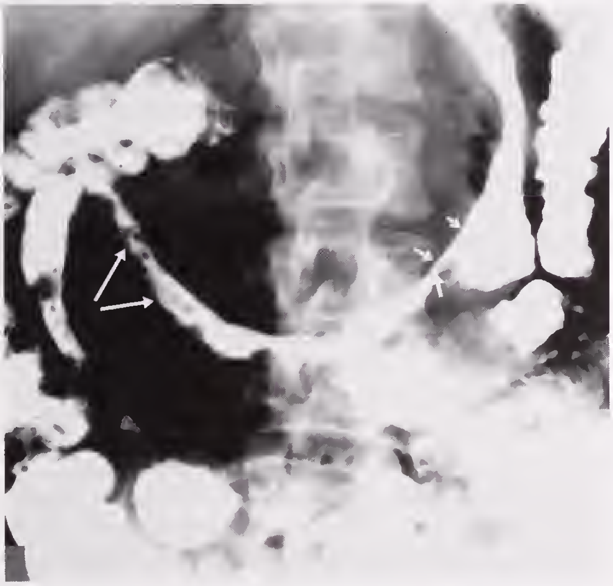

Fig. 2. Stenotic phase of ileojejunitis. The distal jejunum and proximal two-thirds of ileum are involved with alternating areas of narrowing and dilatation (short arrows) with superficial ulceration (long arrows) and separation of the loops.

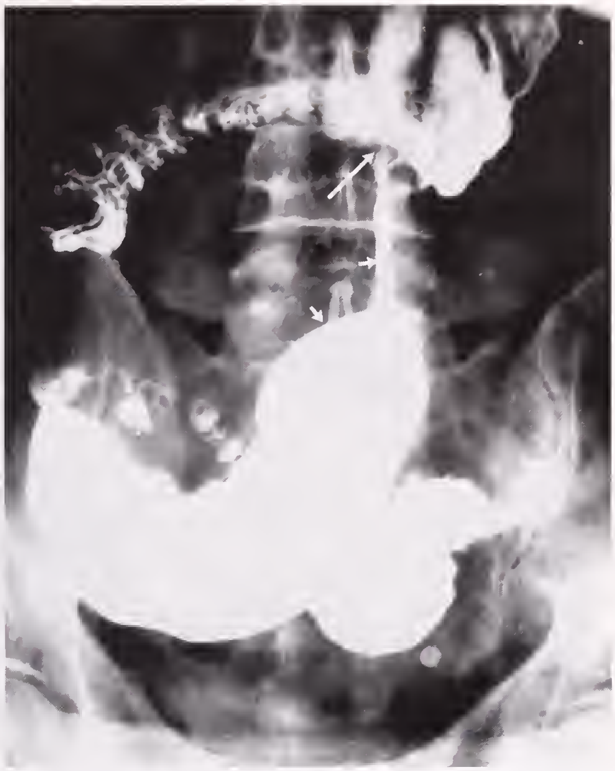

Fig. 3. Recurrent ileitis with marked stenosis and proximal dilatation (short arrows). The patient is status post ileo-transverse colostomy (anastomosis — long arrow).

only inflammatory bowel disease but also such entities as sprue (5) (Figs. 4 and 5), malabsorption (6), protein-losing disorders of the gastrointestinal tract (7), parasitic infestation of the small bowel (8), immunoglobulin deficiency disease (9), vascular disease of the small bowel, including vasculitis (10, 11), benign and malignant tumors of the small bowel (12), small bowel metastases (13) and lymphoma (14). Marshak and Lindner (15) assembled and published, in 1970, the material previously reported. *Radiology of the Small Intestine* became the first standard text of small bowel radiology.

Inflammatory Bowel Disease of the Colon

The Mount Sinai radiologists and gastroenterologists also investigated and described the radiologic changes in inflammatory bowel disease of the colon. Marshak, Wolf and Eliasoph had published "Non-specific Ileocolitis" (16) in 1956 and "Segmental Colitis" (17) in 1959, before the landmark publication of Lockhart-Mummery and Morson's, "Crohn's Disease (Regional Enteritis) of the Large Intestine and Its Distinction from Ulcerative Colitis" in 1960 (18). In these papers, the authors referred to granulomatous disease of the colon and were able to identify the radiologic features which distinguish it from ulcerative colitis.

Early descriptions of other radiologic manifestations of inflammatory bowel disease included a 1950 description of megacolon by Marshak and Lester, reporting a transition from a normal-sized

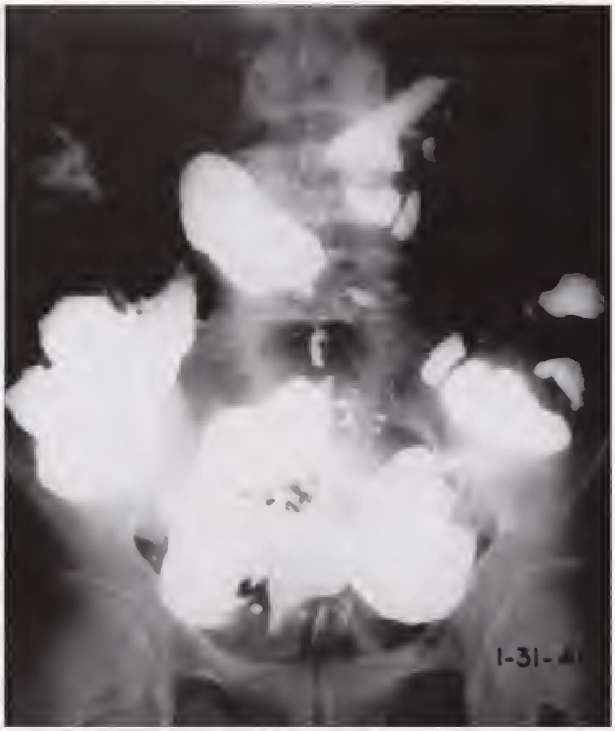

Fig. 4. Sprue. Marked segmentation in association with the moulage sign. Additionally, there is moderate dilatation and hypersecretion.

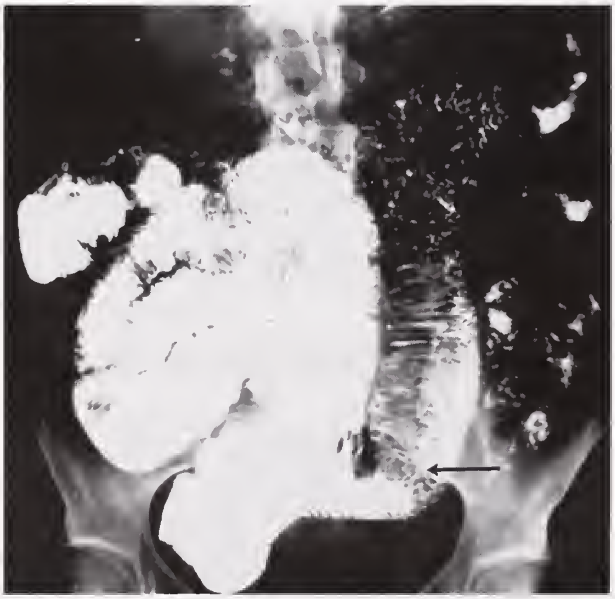

Fig. 5. Sprue. Marked dilatation, flaccidity, flocculation and non-obstructive intussusception (arrow).

bowel in a patient with ulcerative colitis, to subsequent development of toxic megacolon (Fig. 6) (19, 20). The radiologic features of strictures of the colon associated with ulcerative and granulomatous colitis were also presented by Mount Sinai radiologists in 1962. Further studies of inflammatory bowel disease of the colon by Wolf and Marshak in 1962 (21, 22) and by Marshak, Linder and Wolf in 1966 (23) clearly distinguished Crohn's colitis from ulcerative colitis on the basis of their specific radiologic findings.

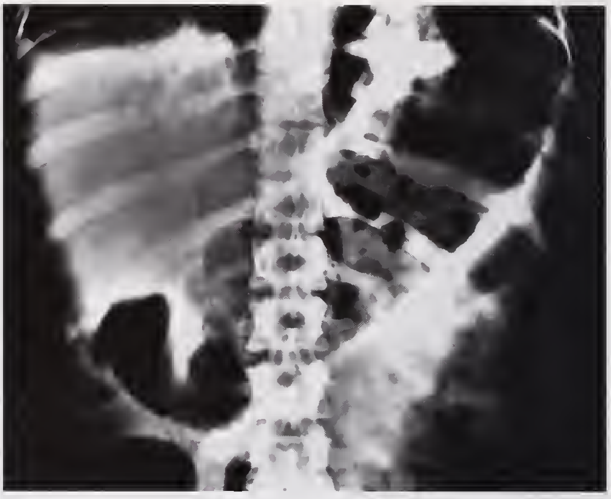

Fig. 6. Megacolon, a complication of ulcerative colitis. There is marked dilatation of the transverse colon with effacement of the haustral pattern and nodularity of the contour.

Other Colonic Disorders

Other disorders of the colon were described by Mount Sinai radiologists, including radiologic findings in diverticulitis with abscess formation and vaginal fistula (1948) (24), diverticulitis and diverticulosis (1957) (25), diverticulitis of the cecum and right colon (1958) (26), lipoma of the colon (1954) (27), scirrhous carcinoma of the colon (1963) (28) and familial polyposis with special emphasis on the differential diagnosis and radiologic features of metastases to the colon, by Khilnani, Marshak, Eliasoph and Janowitz (29) in 1966.

Esophagus

Additionally, Dr. Bernard Wolf was particularly interested in the x-ray demonstration of esophageal disease, beginning with an early description of peptic esophagitis (30), followed by a series of papers, many with Marshak and Khilnani, on the roentgen diagnosis of hiatal hernia (31), contraction ring associated with gross hiatal herniation (32), peptic ulcer of the esophagus and esophagitis with gastric-lined esophagus (33), as well as a description of the gastroesophageal vestibule and its differentiation from the phrenic ampulla and minimal hiatal herniation (34). Wolf's initial description of "use of a one-half inch barium tablet to detect minimal esophageal strictures" (35) presented an objective method for measurement of esophageal strictures (36).

Conclusion

The papers and text described above were important, classical contributions to the understanding of the x-ray findings in diseases of the gastrointestinal tract. In many cases, these primary descriptions acted as a guide to subsequent authors and clinicians during the next three to four decades.

On a personal note, I was privileged to know and work with several of these radiologists who were pioneers in gastrointestinal radiology, including Bernard Wolf, Mansho Khilnani and, most significantly, Richard H. Marshak. Initially, they were my mentors and, later, my colleagues. Although they had different personalities, they all shared a passion for excellence, a remarkable dedication to their work, and intellectual and mental energy to allow them to pursue their goals relentlessly until achieved. Richard Marshak, in particular, was instrumental in advancing small bowel radiology by deciphering the complexities of the follow-through small bowel barium study. In the decades that Dr. Jerold Kurzban and I spent working with Dr. Marshak in his office, we were exposed to an extraordinary spectrum of gastrointestinal radiology, an experience which helped us to maintain the high standards set by our predecessors.

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IBD:

Immunologic Research at The Mount Sinai Hospital

Lloyd Mayer, M.D.

Abstract

An evolution in our understanding of the inflammatory bowel diseases (IBD), ulcerative colitis and Crohn's disease, correlates with increased knowledge of the function of the mucosal immune system. In the early 1960s and 1970s, IBD was considered to be an autoimmune disease in which there was a directed attack by humoral and cellular elements of the immune system against intestinal tissues. These studies did not withstand the test of time, and from the 1970s through the 1990s there was a growing appreciation that defects in cellular immunity, not auto-reactive in nature, played a larger role in disease pathogenesis. Research at Mount Sinai focused in on these cellular T cell defects and helped pave the way for the current model of disease pathogenesis. **Key Words:** IBD, Crohn's disease, ulcerative colitis, immunology, epithelial cells, T lymphocytes.

Introduction

Crohn's disease, as described by Dr. Burrill Crohn and colleagues at The Mount Sinai Hospital in 1932 (1), was initially thought to be an infectious disease, comparable to mycobacterial infections of the intestine, described in the past. The description of Crohn's disease came at a time when there was a limited understanding of the immune system and when genetic diseases were only recognized if they were autosomal dominant or recessive. The concept of a distinct mucosal immune system was decades away, and complex genetic disorders could not even be explored. Still, Crohn and his colleagues were not too far off. As is the case for mycobacterial diseases, the expression of disease relates to the host's response, which is genetically regulated and immunologically mediated. Tools to analyze these latter components of the host response only started to become available in the 1970s as lymphocytes, monoclonal antibodies and cytokines were described. It is only recently that we have had the ability to characterize specific genes, with high throughput technology to map genetic loci.

The end result of these advances is a new hypothesis relating to the pathogenesis of inflammatory bowel disease (IBD). It encompasses many of the components of host response which had previously evoked passionate arguments concerning their validity or regarding the roles of such areas as genetics, environment, immune system, specific pathogens, psychogenic causes, allergies, etc. The current consensus takes many of these factors into account and is built upon an interactive concept. Simply stated, the hypothesis is that in a genetically predisposed host, there is an abnormal immune response to both pathogens and non-pathogens in the gut. IBD is one of many chronic inflammatory diseases known to be multigenic.

Genome-wide screening analyses have identified loci which are IBD generic as well as ulcerative colitis (UC) and Crohn's disease (CD) specific (2–11). It may be that CD and UC involve 5–8 distinct genes and that the nature of the gene defect not only dictates the type of disease but also the subcategory of the disease (e.g., fistulizing vs. inflammatory CD, left sided vs. pancolitis, ileitis vs. segmental colitis). It is plausible that one or more of these genes codes for defects in host defense, as for example, abnormalities in barrier function or defects in mucosal immunoregulation. IBD can be viewed as two events: the trigger or initiating event, and the perpetuation of the immune/inflammatory

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response. Genetic abnormalities may account for one or both of these events.

In early descriptions of CD and UC, emphasis was placed on infectious etiologies. This was plausible, since as alluded to earlier, CD looked like intestinal tuberculosis and UC looked like many infectious types of colitis. However, attempts to define transmissible agents were fraught with poor reproducibility and misinterpreted data. Many of the studies, using stool filtrates from IBD patients to transmit disease into various animal models, reported the ability of an agent in IBD stool to induce colonic inflammation or foot pad granulomas in mice. These were largely the result of reactions to foreign bodies and not a true IBD picture (12, 13). Furthermore, there was the clinical observation that some patients developed IBD following different documented intestinal infections (e.g., post-turista, Salmonella, viral gastroenteritis, etc.). These observations suggested that there may not be a specific infectious cause of IBD, but rather that any infection (in a genetically predisposed host) may result in the initial inflammatory reaction in IBD. Either the persistence of the organism, or defects in regulating the inflammatory response, would result in the perpetuation of the disease. This scenario has recently been validated with studies in a variety of new animal models of IBD, where either barrier function or immune regulation has been altered (see below) (14–29). If these animals are reared in a germ-free environment, they fail to develop colitis (still exposed to dietary antigens — proteins, carbohydrates and lipids) (14, 16, 19, 22, 30–36). If their gut flora is replete with nonpathogenic normal flora (particularly anaerobic flora (*Bacteroides vulgatus*), the disease is expressed. This has been shown to be true in every animal model tested to date, suggesting a uniform role for normal flora in IBD. In fact, one German group has documented a loss of the normal tolerance for autologous flora in patients with IBD (16). These findings suggest that both the initiation and perpetuation of inflammation in IBD relate to an aberrant reaction to the normal constituents in the gut. It places the defect squarely on the shoulders of the host immune/inflammatory response.

Immunologic Research in IBD at Mount Sinai

Role of Cell-Mediated Immunity

How did Mount Sinai contribute to the current paradigm described above? Early studies at Mount Sinai helped switch the focus away from autoimmunity and the role of antibody, to the current focus on cellular or T cell-mediated immune responses. These studies assessed the integrity of T cells in the systemic immune system. The concept at that time was that cells in the peripheral bloodstream might mirror what was actually happening in the intestine. Thus, Sachar and his colleagues (37, 38) assessed skin test reactivity (delayed type hypersensitivity) in patients with UC and CD. They found an increased incidence of anergy (i.e., limited or no skin test reactivity) in these patients, regardless of the site or extent of disease. These studies did not take into account the fact that many of these patients were taking immunosuppressive steroids and/or that their nutritional status (i.e., hypoalbuminemia) might alter the ability of their T cells to function. These questions were addressed in subsequent studies. Meyers et al. (39) asked whether the anergy seen related only to memory responses or whether the T cell defect was more proximal, i.e., the initial T cell response. Using dinitrochlorobenzene (DNCB), a contact skin-sensitizing agent which classically elicits a T cell-mediated delayed-type hypersensitivity reaction, they studied patients and their first-degree relatives for the integrity of their T cell response. As suggested from Sachar's studies, T cell reactivity to DNCB was significantly depressed in patients with both CD (87% reduction) and UC (53% reduction). However, follow-up studies in family members supported the absence of a genetic component. More important, a restoration of T cell reactivity after surgery to remove the affected bowel (although this was more evident in UC patients than in CD) was described. These findings suggested that the defects in T cell reactivity reported by several groups was likely to be secondary to factors reversible by surgery (i.e., reduction in medication, restoration of nutritional status, elimination of inflammation) (40). Other studies by Heimann et al. (41) and Gelernt et al. (42) supported the concept that some restoration of immunological defects in peripheral blood could be achieved following surgical intervention. These studies helped to underscore the need to develop technology to assess immune function in the affected organ, the small bowel and colon.

The Role of the Intestinal Epithelium in Mucosal Immunoregulation

Moving into the gut meant that the normal mechanisms of mucosal immunoregulation needed to be defined. Several groups had already reported that the lymphoid populations in the gut were quite different from those of the systemic immune system. It was also clear that the stimulus for an immune response (antigen [Ag]) was going to be distinct from Ag given intramuscularly or subcutaneously, given the fact that antigens in the gut lumen were subject to extremes of pH, proteolytic enzymes, etc. In addition, sites of Ag uptake in the gut were clearly distinct from those in lymph nodes and spleen. With this as a background, Mayer and Shlien (43) first described a novel role for human intestinal epithelial cells (IEC), that of antigen-presenting cells (APC) which could process and present Ag to T lymphocytes. However, unlike conventional APC (macrophages/dendritic cells/B cells), T cells proliferating in response to Ag presented by isolated IEC were found to be CD8$^+$ Ag-nonspecific suppressor T cells. This discrepancy was quite unusual, given the fact that IEC express restriction elements (major histocompatibility complex [MHC] class II molecules) which typically interact with and activate CD4$^+$ T cells. Over the past decade, the mechanisms involved in this selective activation have been defined. IEC express nonclassical class I molecules such as CD1d, which are capable of activating suppressor T cells (44). However, CD1d, cannot perform this function alone. Yio and Mayer (45) described an epithelial surface glycoprotein, gp180, which is expressed on normal IEC, binds to CD8 and promotes the activation of CD8$^+$ T cells. gp 180 binds to CD8 at sites which are distinct from those used by classical class I molecules (human leukocyte antigen [HLA] — A, B, C) and, therefore, does not interfere with the function of CD8$^+$ cytolytic T cells. This glycoprotein is, however, a critical component in the activation of CD8$^+$ suppressor T cells. While an *in vivo* model supporting this role for IEC has not been clearly defined, there are a large number of *in vivo* and *ex vivo* studies which support such a role for IEC. The activation of CD8$^+$ T cells locally could explain the local, controlled, physiologic inflammation seen in the gut. Thus, Ag sampled via the IEC would result in a suppression of local responses.

Defects in IEC Function in IBD

How does this relate to IBD? In 1990, Mayer and Eisenhardt (46), using the IEC co-culture system, reported that IEC derived from patients with UC and CD failed to activate CD8$^+$ suppressor T cells. Importantly, this defect was noted regardless of where the tissue used to isolate the IEC was derived (i.e., both inflamed and noninflamed tissue). This suggested that the defect in CD8$^+$ T cell activation might be more generic. In 1997, Toy et al. (47) provided an explanation for these *in vivo* studies. Using an antibody against gp180, derived in the laboratory, they noted that defects in the expression of this molecule existed for both CD and UC. However, the defects were different. In UC there was an alteration in the form of gp180 expressed (apical and not basolateral), and in CD there was a marked decrease in total expression. The end result would be the same. If there was no interaction of gp180 with T cells, no CD8$^+$ suppressor T cells would become activated. In fact, the enhanced class II Ag expression on the cells, described by Mayer et al. (48) and others, helped to promote proliferation of CD4$^+$ T cells in these co-cultures. The failure of suppressor mechanisms in IBD is not a new concept. Several groups have suggested this from studies in peripheral blood, including Godin et al. (49), who documented an increase in the percentage of CD4$^+$ T cells in the peripheral blood. Without regulation, CD4$^+$ T cell activation by luminal antigen might continue to go on unabated, with perpetuation of inflammation.

The aberrant activation of CD4$^+$ T cells can have several consequences, the first being increased cytokine production. Mount Sinai has approached this prospect in two ways: direct measurement of cytokine in diseased tissue and the use of therapies which alter cytokine production or function. In the first case, Salomon et al. (50) measured γ-interferon (γ-IFN) production by lamina propria lymphocytes from normal patients and disease controls. In both UC and CD, there was a marked increase in γ-IFN production. Given the marked inflammatory nature of this cytokine, its presence clearly helped to explain many of the reported phenomena, including macrophage activation, enhanced class II expression on IEC, etc. (48). Therapies directed against cytokines are also a useful tool to define mechanisms. Lichtiger et al. (51) published the results of a trial of IV cyclosporin in patients with presurgical UC. The initial results were outstandingly successful, eliminating the need for colectomies in more than 80% of patients. Cyclosporin is a potent inhibitor of cytokine synthesis, particularly IL-2. The prototype anti-cytokine therapy is the newly approved anti-tumor necrosis factor (TNF) mAb (infliximab). TNF, produced by activated macrophages and T cells, may also explain several of the histopathologic features of CD. Neutralization of TNF or alteration in the cells producing TNF can have prolonged salient effects on these patients (52–54). Thus, targeting the effects of aberrantly activated T cells may be quite effective in modulating the disease. The identification of these cells may be one way of accomplishing this therapeutic effect. In a series of studies by Shalon et al. (55) and Posnett et al. (56), it became clear that the population of CD4$^+$ T cells present in the gastrointestinal tract of patients with CD was clearly altered compared to normal controls. While the function of these expanded populations was not addressed, it was postulated that these may represent the aberrantly activated T cells described above. Studies to define the true nature of these populations are in progress.

Cytokines produced by these activated T cells may also alter the function of other cells in the mucosal environment. Focusing on the effects of cytokines on the epithelium, Panja et al. (57) defined receptors for inflammatory cytokines expressed by IEC derived from normal controls as well as from patients with IBD. While there is an increase in the number of these cytokines in the mucosa, there is no increase in receptor expression. This suggests that the epithelium in IBD patients is not more sensitive to inflammatory cytokines but may be reacting to the altered cytokine environment. The effects of the increased concentration of cytokines are evident. mRNA for a variety of growth factor receptors was reduced in IEC derived from IBD patients (EGF-R, IGFI-R, CSF1-R, and PDGF-R-beta) (58), and the steady-state levels of transcripts of H-ras and five nuclear proto-oncogenes (c-myc, c-fos, c-jun, junB, and N-myc — involved in cell cycle) were lower in epithelial cells from involved or uninvolved IBD samples than in normal epithelial cells from patients with either sporadic colon cancer or diverticulitis (59). These findings might be of significance with regard to the increased incidence of adenocarcinomas reported in both CD and UC. These inflammatory cytokines may also play a role in inducing or suppressing other mediators important for mucosal integrity. Sperber et al. (60, 61) described a novel mucin secretagogue, MMS-68, which stimulates mucin secretion by intestinal and airway epithelial cells. When studying patients with IBD, they found that there was a decrease in the level of expression of MMS-68 in their tissues. Altered mucin production has been described in IBD and may be an important contributor to the defects in barrier function described in these diseases. Such a defect could result in the enhanced transmigration of bacteria from the lumen into the mucosa-associated lymphoid tissue, allowing for persistent inflammation.

When viewed in composite, the studies from Mount Sinai have suggested defects in the initial activation of important regulatory cells following antigen challenge. These defects are then magnified by the establishment of a cytokine environment which promotes further inflammation and tissue destruction. The IEC may be a focal point for many of these pathways. Correcting these defects and/or reducing their effects on the epithelium may be a viable approach to novel therapies.

Summary

The concept that IBD represents an aberrantly stimulated or poorly regulated CD4$^+$ T cell response is growing in strength. *In vivo* and *in vitro* data attest to its validity. Animal models of either T cell dysregulation or altered barrier function develop IBD. Those with B cell defects or defects in nonregulatory T cell subpopulations do not. The *in vitro* and *in vivo* data are starting to coalesce. What is likely to emerge is that adaptive immune, nonimmune and innate immune responses play a role in concert in the development of IBD. These types of studies are ongoing.

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A History of Immunosuppressive Drugs in the Treatment of Inflammatory Bowel Disease:

Origins at The Mount Sinai Hospital

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Abstract

Much of what we know about the role of immunopathologic mechanisms in causing Crohn's disease and ulcerative colitis originated from research at The Mount Sinai Hospital. The authors were privileged to have been able to share in this undertaking, along with many others, including Moschcowitz, Klemperer, Otani, Crohn, Ginzburg, Oppenheimer, Garlock, Lyons, Marshak, Janowitz, Aufses, Waye, Greenstein, Sachar, Meyers, Gelernt, Mayer, Lichtiger and Kornbluth.

In medical history, elucidation of disease processes is often serendipitous. Transplant surgery was successful because of the discovery by Hitchings and Elion of 6-mercaptopurine (6-MP) and azathioprine, which inhibited rejection. And the concept of immunosuppression slowly evolved into possible treatment of any disease thought to be caused by autoimmunity. This includes those diseases of the bowel seen so frequently at The Mount Sinai Hospital: ileitis, granulomatous colitis, ileocolitis, and ulcerative colitis.

This paper depicts the progressive role of immunosuppressive drugs, from corticosteroids to 6-mercaptopurine, cyclosporine and anti-tumor necrosis factor, in both the treatment and understanding of the pathogenesis of Crohn's disease and ulcerative colitis. Major contributions to these treatments have come from physicians and surgeons with roots at The Mount Sinai Hospital. **Key Words:** Immunosuppressive drugs, 6-MP, cyclosporine, anti-tumor necrosis factors, IBD.

When we arrived at Mount Sinai, several decades had already passed since the landmark publication on regional ileitis by Crohn, Ginzburg, and Oppenheimer (1). Management remained primarily in the hands of the surgeons. Drug therapy had been limited to a variety of sulfonamides, and gastroenterologists were slow to acknowledge that one (sulfasalazine) differed from all the others, and should be favored. Even so, sulfasalazine did not work as well in ileitis as it did in ulcerative colitis. The morbidity and surgical incidence for both diseases remained high and the mortality rate, particularly for children with ulcerative colitis, was unacceptable (2).

In 1949, the first edition of Dr. Crohn's book (83) included data on the course, complications, and treatment of ileitis. Corticosteroids, which became available soon thereafter, were not mentioned at all. Yet, never before had such dramatic improvements been seen as those that followed treatment with corticosteroids and corticotropin. The outcome was influenced so favorably that surgery could now be postponed and performed electively. The gastroenterologist inherited the primary responsibility for patient management and clinical observation (3).

In retrospect, this period was one of relative complacency, particularly with regard to the search for new drugs. The initial euphoria, although warranted by the success of the steroids in eliminating the inflammatory process, yielded to the sober realization that the effect was transient (4) and that the inflammation returned not only with discontinuation of the drug but even with dose reduction. Also, the inflammation responded less dramatically with subsequent courses of treatment; finally, corticosteroids were shown to be no more effective than placebos in

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maintaining remission (5). They also had the potential for major toxicity.

In the 1960s, the following factors rekindled an effort to provide new treatment for inflammatory bowel disease (IBD):

1. The causes remained unknown.
2. The concept of autoimmune diseases began to be appreciated (6, 7).
3. The question was frequently raised as to whether Crohn's disease and ulcerative colitis could be autoimmune diseases.
4. Studies demonstrating auto-antibodies in ulcerative colitis were being reported (8).
5. Azathioprine was shown to inhibit rejection of the donor's transplanted kidney (9).
6. Toxicity due to corticosteroids was reported (10).
7. Winkelman and Brown (11) reported a favorable experience with nitrogen mustard in the treatment of both ulcerative colitis and regional enteritis.
8. Bean had successfully treated an ulcerative colitis patient with 6-mercaptopurine (12), a metabolic product of azathioprine, and was pursuing this early success (13).
9. Brooke et al. (14, 15) reported previously unheard-of reversals of advanced Crohn's disease, including those with complex fistulas, when patients were treated with azathioprine after all surgical efforts had failed.

Although later epidemiologic data showed that the incidence of Crohn's disease was on the rise whereas the incidence of ulcerative colitis was stable, this was not yet apparent in the 1960s. One of us (BIK) had seen many ulcerative colitis patients with Banks and Zetzel at the Beth Israel Hospital in Boston (16). At Mount Sinai, he was disturbed by the large number of children with ulcerative colitis in whom corticosteroid therapy had failed, who were physically and emotionally traumatized by the toxicity of these drugs, and who required colectomy and ileostomy (with high mortality) (3, 17). In view of this experience, in January 1967 it was decided to add 6-mercaptopurine (6-MP) to the treatment of ulcerative colitis patients who had not responded favorably to corticosteroids and sulfasalazine treatment, and who did not have an absolute indication for surgical intervention (18).

The co-worker in this study (18) was Nathaniel Wisch, a hematologist, who favored 6-MP over azathioprine (azathioprine is converted to 6-MP *in vivo)* only because he had had experience with its use in treating childhood leukemia. Furthermore, the Food and Drug Administration had approved 6-MP for use in the treatment of that disease. At the conclusion of this study, it was clear that 6-MP had no dramatic short-term influence on the course of the disease; moreover, transient nausea and vomiting occurred frequently. Apparently, 6-MP had no role in the treatment of fulminating ulcerative colitis or toxic megacolon. This finding confirmed those already demonstrated for azathioprine by Bowen et al. (19), who suggested that immunosuppressive drugs should not be used for the treatment of ulcerative colitis. Nonetheless, we had noted favorable results in a select group of patients, which led us to adopt new criteria for instituting 6-MP therapy. Our choice of candidates included those with chronic prolonged ulcerative colitis, those who had an incomplete response to steroids, those who had complications from the steroid treatment, those who had contraindications to the use of steroids, and those in whom sulfasalazine had failed.

Perhaps the most important observation we made was that the real value of 6-MP could only be determined after long-term observation. We found that 13 of 14 patients either went into remission or improved significantly; only one remained incapacitated. Based on this study, and our later experience when the series had been expanded to 25 patients (20), a long-term, double-blind, controlled study was planned.

Coincidentally, in the late 1960s the following events occurred:

1. One of us (DHP) completed his fellowship in gastroenterology at Mount Sinai. In addition to the teacher (BIK)-student (DHP) relationship, we became friends and found that we shared common interests in clinical investigation of IBD. We were both enthusiastic about conducting a double-blind trial of immunosuppressive therapy.
2. The Ileitis Foundation was launched by Irwin Rosenthal, William Modell, and our Chief of Gastroenterology at Mount Sinai, Henry D. Janowitz. The primary goal of the foundation was to encourage and support research in

IBD, and DHP became its first fellow and research grant recipient. The early participation of BIK was encouraged by the founders because of his accumulated experience with ulcerative colitis. Soon thereafter, the name of the organization was changed to the National Foundation for Ileitis and Colitis.

3. Dr. Janowitz suggested that the protocol place more emphasis on Crohn's disease than on ulcerative colitis. It was already known that ulcerative colitis is premalignant, and there was some concern that immunosuppressive drugs might provoke an earlier onset of neoplasia. It was not yet known that Crohn's colitis also predisposed to the development of colon cancer. Also, we knew that a colectomy "cured" ulcerative colitis, but Crohn's disease recurred in most patients after surgical resection.

Crohn's Disease

In 1969, we launched a 2-year, placebo-controlled, double-blind, crossover study of 6-MP in the treatment of refractory Crohn's disease (21). Because there were no prior indices to measure the remission of Crohn's disease, we established our own for the controlled trial. These included "goals" of therapy for each case, as was done in the usual clinical management of Crohn's disease. We felt then, as we do now, that Crohn's disease has many diverse presentations and that this "goal index" was the most accurate way to interpret clinical responses in patients with chronic refractory disease. The most common goals were:

- elimination of corticosteroids
- closing of fistulas
- prevention of small bowel obstruction

Elimination of the primary bowel symptoms alone was not an objective, because steroid treatment temporarily accomplished this. Rather, symptoms had to be alleviated after stopping the steroids, which would indicate that 6-MP had been effective. It should be noted that although this study was initiated in 1969, it was until recently the only randomized controlled trial for treatment of fistulas in Crohn's disease, despite the fact that one-third of Crohn's disease patients have evidence of fistulization. Although initiated after our study was started, the National Cooperative Crohn's Disease Study (NCCDS) was then being conducted at 14 other medical centers. In that study, the newly developed Crohn's Disease Activity Index (CDAI) was used as a measure of response to compare prednisone, sulfasalazine, azathioprine, and placebo (22, 23), and showed that azathioprine was ineffective (22). Based on the results of our own ongoing study, we and others submitted a critique of the NCCDS study, pointing out its shortcomings (24, 25). Although the results of the NCCDS study were presented at the plenary session of the annual meeting of the American Gastroenterological Association (AGA) in 1980, our own abstract was not scheduled for presentation at that time. Rather, it was scheduled for presentation one day later and at a smaller forum. At our presentation, we encouraged clinical researchers not to abandon the use of immunosuppressive drugs in this disease, and stated that physicians in private practice were capable of contributing significantly in the performance of randomized clinical trials. The basis of our concern regarding the outcome of the NCCDS study was the following:

1. The study terminated prematurely at 17 weeks, too soon for many patients to respond.

2. It eliminated azathioprine because it caused pancreatitis in a few instances. Consequently, there were insufficient entries assigned to azathioprine to reach statistical significance.

3. It withdrew steroids before starting the assigned drug or placebo, thereby enhancing the likelihood of exacerbating the underlying disease.

4. The dose of azathioprine used was relatively small.

In 1980, our own study was published and showed conclusively that 6-MP was effective in the treatment of Crohn's disease (21). The following is a list of the clearest results of the study:

1. The overall success rate was greater than 66%. Of the 39 patients who participated in each year of the 2-year crossover study in which either 6-MP or placebo was administered throughout one full year, the outcomes were significant ($p < 0.0001$) (Table 1).

2. Thirty-three (33) patients completed only one year (refusing to cross over) and therefore received only one drug, either 6-MP or placebo; for the 19 receiving 6-MP, the rate of

TABLE 1
Results in 39 Crossover Patients

	Number of patients	
Treatment	Improved*	Not improved
6-MP	26/39	13/39
Placebo	3/39	36/39

*Whereas 67% of the patients improved with 6-MP, only 8% improved with placebo. The difference is 59% with 95% confidence limits of 32 to 86% ($p < 0.0001$).

improvement was 79% as compared with 20% of the 14 patients treated with placebo ($p < 0.05$) (Table 2).

3. To determine whether the outcome of the first year of trial influenced the outcome of the second year, a separate analysis was performed for 36 patients. There was a highly significant difference for the patients receiving 6-MP, with improvement in 67% vs. 14% of patients treated with placebo ($p < 0.0001$) (Table 3).

4. In the study, steroids were completely eliminated in 55% of the patients, or the dose of steroids could be reduced by 20%.

5. The healing of fistulas was accomplished. Closure of fistulas occurred in 24% compared with placebo closure of 6%.

6. The study confirmed that the drug was slow acting (mean response time of 3.1 months) and in many instances, patients required continuation of steroids. Almost 20% of patients who would ultimately respond had not done so at 17 weeks, the time at which the NCCDS already had been completed.

TABLE 2
Results in 33 Noncrossover Patients

	Number of patients	
Treatment	Improved*	Not improved
6-MP	15/19	4/19
Placebo	4/14	10/14

*Whereas 79% of the patients improved with 6-MP, only 29% improved with placebo. The difference is 50% with 95% confidence limits of 20 to 80% ($p < 0.05$).

TABLE 3
Combined Results during First Year

	Number of patients	
Treatment	Improved*	Not improved
6-MP	26/36	10/36
Placebo	5/36	31/36

*Whereas 72% of patients improved with 6-MP, only 14% improved with placebo. The difference is 58% with 95% confidence limits of 40 to 77% ($p < 0.001$).

7. Drug toxicity was modest and there was no early mortality.

Expanded data on fistulas of different sites followed (26). 6-MP seemed to close fistulas in one-third of the patients and it meaningfully reduced discharge from fistulas in another third, with a mean response time of 3.5 months. 6-MP (and azathioprine) proved to be the first drug to have this influence on fistulas in Crohn's disease, with the sole exception of metronidazole, which had a favorable effect only on perirectal fistulas. There has never been a controlled-trial confirmation of the efficacy of metronidazole on fistulas; in our clinical experience, many patients relapse after prolonged use of this antibiotic. Many also develop peripheral neuropathy. Abdominal wall fistulas improved or closed in 10 of 12 cases (83%), rectovaginal fistulas in 4 of 6 (67%), and enteroenteric fistulas in 5 of 7 (71%). Patients with perirectal abscesses and fistulas sometimes had diversionary operations, such as a colostomy or ileostomy. The results in many cases were disastrous, with recurrent Crohn's colitis in the stoma, diversion colitis in the rectum, and persistence of perirectal sepsis. A modified Parks' operation combined with 6-MP eradicated many perirectal abscesses and fistulas in those patients with recurrence after an incision and drainage procedure (27).

Our early observations noted that the use of immunosuppressive drugs was apparently more effective in the treatment of Crohn's disease when the colon (ileocolitis or colitis) and small bowels were both involved, rather than the small bowel alone. O'Donoghue et al. (28) had shown that the one-year remission, once established, was maintained by azathioprine in 95% of the patients compared with 59% on placebo. Early observations after completion of our own controlled trial showed maintenance of remission in 19 out of 20 patients (95%) after a mean of 37 months on 6-MP. After stopping 6-MP therapy, 81% of the 32 patients who had been studied relapsed after a mean interval of 6 months. When 6-MP was reintroduced in 16 of these patients after relapse, improvement was noted within a mean response time of 1.5 months, considerably more rapidly than had been the case for their first response (29).

Subsequently BIK and his colleagues at Lenox Hill reported a long-term experience with

6-MP in the treatment of Crohn's disease (30). Again, therapeutic goals were established for each of the 148 patients, and an index of Crohn's disease activity was calculated both before and after therapy. The goals, as defined previously, were achieved in 68% of cases. Major successes included elimination of steroids (66%; $p < 0.001$) and healing of internal fistulas and abscesses, with elimination or reduction in drainage and tenderness (64%; $p < 0.05$). Moreover, healing or marked improvement was noted in all cases of Crohn's disease involving the stomach and duodenum. Elective surgical resection was made much easier, if and when it had to be performed after 6-MP therapy, because the margins separating normal and diseased tissue were delineated much more clearly. However, prevention of recurrent small bowel obstruction and disappearance of abdominal masses were noted in only 43% and 55% of the cases, respectively.

Ulcerative Colitis

After the early success by Bean (12, 13) in the treatment of ulcerative colitis with 6-MP, uncontrolled trials of immunosuppressives in ulcerative colitis reported response rates of 70–80%. There was less enthusiasm for initiating controlled trials in ulcerative colitis than in Crohn's disease, due in part both to the risk of carcinoma of the colon and the knowledge that ulcerative colitis could be "cured" by colectomy. Furthermore, those who did undertake controlled trials of ulcerative colitis reported disappointing results, with one exception. In that study, it was noted that azathioprine permitted a significant reduction in steroid dosage (31).

Present et al. first reported, in an abstract in 1988 (Gastroenterology 1988; 94:A359), a good-to-excellent response to 6-MP in 25 patients (73%). The mean time to the response was 2.3 months. A subsequent report from Mount Sinai in 1996 (32) showed complete remission in 68 of 105 patients (65%) and partial remission in 25 (24%) with 12 (11%) failures. Although 6-MP was maintained, subsequent relapse was seen in 35% of the patients. In this group, steroids were required in 12% to restore remission. Fifteen (15) patients stopped 6-MP electively and 13 relapsed after a median interval of 14 months. Thus, it was recognized that maintenance 6-MP was important after patients had responded favorably.

Adler and Korelitz (33) reported the results of 87 patients refractory to steroids who had been treated with 6-MP. In 42 patients (48%), steroids could be eliminated, with good control of symptoms after a mean treatment period of 2.5 months. The mean steroid-free period while on 6-MP was 10.9 months. Eleven cases (13%) demonstrated an intermediate but significant reduction in steroid usage.

Hawthorne et al. (34) reported the results of a randomized, 1-year, controlled-withdrawal study of azathioprine vs. placebo involving 67 patients with ulcerative colitis who had been taking azathioprine for 6 months or longer. In the 2-year interval, 59% of those switched to placebo relapsed, in contrast to 36% of those maintained on azathioprine ($p = 0.04$).

Despite the lack of controlled trials, it has been our experience that 6-MP has proven to be both safe and effective in treating severe chronic ulcerative colitis. We have been able to avoid urgent surgery in more than 75% of cases. In many cases, surgery had been recommended without making the patient aware of the efficacy of 6-MP. Perhaps to some physicians and surgeons, this is justified by the advent of the ileal pouch-anal anastomosis. This position, however, has been compromised by the lack of universal and consistent success with this procedure (mean technical failure rate of 6%) and the inability to predict which patients will do well and which patients will exchange one affliction for another (chronic pouchitis in 6–8%) (35–37).

Toxicity of Immunosuppressive Agents

Historical Aspects

Experience with 6-MP and azathioprine has shown that bone marrow suppression can occur and is dose related. Both leukopenia and thrombocytopenia have been reported. Hepatotoxicity is seen less frequently.

6-MP and azathioprine can cause chromosomal aberrations in animals and humans, but these are reversible in humans. The drugs are carcinogenic in animals at the dosages used and therefore may theoretically increase the risk of neoplasia in humans. Again, the risk has been greater in transplant cases than in autoimmune disorders such as rheumatoid arthritis, perhaps because of the higher doses used.

Allopurinol, used to lower blood uric acid, may retard the catabolism of 6-MP and accentuate its toxicity. When the two drugs are used concurrently, the initial dose of 6-MP should be reduced by at least one third.

Toxicity to 6-MP in IBD has been compiled for 396 patients seen by the authors in their private practices (38). Four types of toxicity directly attributable to 6-MP have been identified. These are pancreatitis, bone marrow depression, idiosyncratic and/or hypersensitivity reactions, and drug-induced hepatitis.

Data on all toxicity to 6-MP has been updated since the earlier report, providing a larger number of IBD patients followed for longer periods of time with similar outcomes (39).

Pancreatitis. Pancreatitis after 6-MP was observed in 12 of 396 (3%) patients with Crohn's disease and one with ulcerative colitis (40). The peak incidence was 21 days after starting the drug, and all but one case occurred within 32 days. Clinically, each case was mild, with symptoms of abdominal pain, nausea, vomiting, and elevation of serum amylase, all resolving quickly upon discontinuation of the drug. No hemorrhagic pancreatitis, hypocalcemia, pancreatic abscess, or pseudocyst formation was observed. Seven patients were later rechallenged with 6-MP or azathioprine, and in each, the symptoms recurred rapidly. Clinically, the pancreatitis behaved like a sensitivity reaction, but attempts at desensitization were unsuccessful. Therefore, a single bout of 6-MP pancreatitis is considered a contraindication for future use, but a trial using small doses of azathioprine may be clinically warranted.

Bone Marrow Depression. In 2% of patients, bone marrow suppression sufficient to necessitate hospitalization occurred during the early years, before experience was gained in blood count monitoring and individual dosage adjustment (38). In these 8 patients, the lowest white blood count ranged from $300-2500/mm^3$. Fever was present in 7, and blood cultures were positive in 3. Major septic complications were seen in one patient, but there were no deaths. Characteristically, the bone marrow depression was usually followed by prolonged remission of Crohn's disease or ulcerative colitis. This observation has also been noted by others in relation to ulcerative colitis (41). Leukopenia was noted in most patients at some time. White blood counts above $3500/mm^3$ were rarely associated with clinical problems and were managed by temporarily stopping the 6-MP and then resuming it at a lower dosage.

Subsequently, Connell et al. (42) reported the experience from St. Mark's Hospital, London in 739 patients with IBD treated with azathioprine. Only 9 (1.2%) developed severe leukopenia (white blood cell count $< 2000/mm^3$); 5 of the 9 patients had complications which resulted in 2 deaths. Neither of the deaths was predictable, based on monitoring of the white blood cell count. Our own experience suggests that current methods of monitoring are adequate and that this severe complication is rare and may be modified by the availability of the colony-stimulating factor.

Idiosyncratic/Hypersensitivity Reactions. In addition to pancreatitis, other allergic type reactions occurred within the first 3 weeks of treatment with 6-MP in 2% of patients: drug fever was seen in 8, skin rash in 2, arthralgia in one, and abdominal pain with normal serum amylase in one. We have also seen severe muscle pain soon after initiating treatment with 6-MP. Rechallenging with 6-MP or azathioprine produced similar reactions. Nevertheless, desensitization with gradually increasing doses has often allowed reinstitution of a drug without recurring adverse reaction (43). Whether these reactions are idiosyncratic or represent an allergic phenomenon is unknown, because no definitive immunologic hypersensitivity mechanism has been defined.

Recent data confirm the proportion, nature and outcome of allergic reactions to 6-MP, including the usual failure of desensitization to tiny doses, but occasional success with crossover to AZA (44).

Drug-Induced Hepatitis. Eleven patients in this study developed a type of hepatitis (38), but in only one patient could it clearly be attributed to 6-MP. For this patient, who had severe ulcerative colitis that had remitted, results of liver function tests returned to normal after the drug was discontinued. These same tests became abnormal again after rechallenge. This is the only allergic-type form of toxicity that seems to occur late in the course in most cases. Hepatitis is also unique in that rechallenge is often tolerated. The only instance of immediate toxicity occurred at a later date in a patient whose 6-MP was initiated at 3 mg/kg of body weight. Recent studies have shown that abnormal liver function tests are often associated with high levels of 6-MP, which return to normal when doses are lowered.

Infections

Almost every type of infection reported in patients with IBD treated with 6-MP has also been reported in patients not treated with immunosuppressive drugs. This is especially true of patients with Crohn's disease, in which infectious complications are frequent.

All our patients receiving 6-MP who developed fever were instructed to discontinue the drug regardless of whether we thought the fever was related to the underlying bowel disease, the drug, or an incidental illness such as an upper respiratory tract infection or a viral infection. Two patients developed liver abscesses that required drainage.

Five patients developed pneumonia; all responded to antibiotics and cessation of 6-MP therapy. Some patients with pneumonia responded equally well to antibiotics while continuing 6-MP. Some patients reported frequent colds and upper respiratory tract infections, and elected to discontinue 6-MP. It is difficult, however, to document any increased incidence of respiratory infection.

Herpes zoster occurred in 8 patients while they were taking 6-MP. In all cases, the "shingles" took its usual course. Many years later, one patient had a recurrence of herpes zoster on his trunk when he was again taking 6-MP, and also suffered a 3-day syndrome consistent with encephalitis. There has been no residual defect during a 9-year follow-up, and the patient's ulcerative colitis has remained in remission. Subsequent experience suggests there is no advantage to stopping the 6-MP during the course of herpes zoster if it is mild. When shingles is severe, the 6-MP should be stopped and then reintroduced after a benign course is confirmed (45).

Neoplasms

The situation in regard to neoplasms is similar to that with infections. Neoplasms occur more frequently in patients with IBD whether they have received immunosuppressive medication or not. In Crohn's disease particularly, an increased risk of extraintestinal neoplasms has been recognized (46). An appraisal of neoplastic risk was made for our patients during or after 6-MP therapy (38), and in one instance, the neoplasm was considered to be probably related to the 6-MP. This tumor was a diffuse cerebral histiocytic lymphoma in a man with Crohn's disease, who had taken 6-MP for approximately 9 months. The drug had been discontinued 11 months before the onset of headaches and the discovery of the tumor. The tumor did not respond to therapy. Two more cases of cerebral lymphoma in patients with Crohn's disease treated with azathioprine have subsequently been reported (47).

Other neoplasms occurring in patients who had earlier received 6-MP included an islet cell carcinoma of the pancreas, carcinoma of the lung in a heavy cigarette smoker, one carcinoma of the breast, and a basal cell carcinoma. One patient with ulcerative colitis developed malignant melanoma; an excision with an axillary node dissection was curative. We have subsequently seen three patients who developed carcinoma of the breast 5, 25, and 27 years after first receiving 6-MP.

Two simultaneous carcinomas of the colon occurred in one patient with long-standing ulcerative colitis who had refused the recommendation of colectomy. In these cases, the carcinomas clearly anteceded the initiation of 6-MP. Subsequently, one additional patient with long-standing left-sided ulcerative colitis, who had received 6-MP for one year, developed a carcinoma of the rectum. Benign adenomatous polyps have been encountered on sigmoidoscopy or colonoscopy in patients receiving 6-MP; the polyps have been removed endoscopically and no recurrence has been encountered despite continuation of 6-MP.

Cancer of the colon could be a complication of particular concern, because both ulcerative colitis and Crohn's colitis are diseases prone to the development of cancer even without immunosuppressive drugs. We reviewed our own experience and counted 34 patients with cancer of the colon following ulcerative colitis, during a 20-year period; two patients had taken 6-MP and 32 had not. As for cancer of the intestinal tract complicating Crohn's disease, we identified 17 patients in whom carcinoma of the ileum or colon developed; only two had been treated with 6-MP. Although these figures are not controlled and do not include a denominator, carcinoma seems to be far more common in Crohn's disease and ulcerative colitis independent of immunosuppressive therapy than associated with it. Subsequently, Connell et al. (48), reporting their data from St. Mark's, also concluded that the incidence of colorectal cancer and death from cancer in patients with IBD who had been treated with azathioprine is not greater than in those patients who had not been so treated.

Recent data from the IBD Center at Lenox Hill Hospital confirm the earlier observations of no increase in neoplasms in patients with IBD who have been treated with 6-MP or AZA (49). Nevertheless, concern persists as to whether the onset of a neoplasm is accelerated, but there are no controlled data to answer this question. Currently one of us (BIK) is investigating the possible role of sustained leukopenia as a contributing factor.

Nausea

Nausea is seen as a fairly common side effect during the first month of therapy. Occasionally the dose of 6-MP has to be temporarily reduced. Rarely does the drug need to be eliminated on this basis.

Mortality

With the single exception of the patient with cerebral lymphoma, no deaths were attributable to 6-MP. Lymphomas of the brain (50) and other lymphomas (51) also have been reported in transplant patients on immunosuppressive therapy. Although it is most likely that these tumors were caused by 6-MP, two reports (52, 53) suggest an increased incidence of lymphomas in patients with Crohn's disease who were not taking immunosuppressives.

Considerations in Pregnancy

6-MP and azathioprine cause reversible chromosome damage in humans, but the true teratogenic effect of these drugs has not been studied in a systematic or controlled manner. On theoretical grounds, most obstetricians have advised that conception is contraindicated for both women and men receiving 6-MP. We advise chronically ill female patients with persistent bowel activity not to become pregnant. Therefore, before initiating 6-MP therapy, a female patient should have her serum tested for human chorionic gonadotropin level to eliminate the possibility of early pregnancy. All couples are instructed to practice a reliable method of birth control. The authors (BIK and DHP), however, differ with respect to the continued use of maintenance 6-MP therapy after suitable remission in patients who want to become pregnant.

When pregnancy becomes a priority, BIK recommends stopping 6-MP before discontinuing contraception. In a toxicity study (38), the authors found that 16 pregnancies had occurred. In 10 patients, 6-MP had been terminated before contraception. In the remaining 6 patients, 6-MP had been continued for 3–4 weeks before the pregnancy was recognized. In 3 of the 6 patients, as well as the 10 who stopped 6-MP earlier, the pregnancies were continued. All 13 patients delivered full term. No abnormalities have been found in any of the 13 children. Additional data reported from St. Marks support the conclusion that there is little danger to the mother or the fetus by taking azathioprine throughout pregnancy (54).

A recent extensive study of DHP's patients compared the outcomes of 240 live births from 155 patients with IBD who had either stopped 6-MP before conception, or had conceived while taking 6-MP, and then either stopped or continued the drug throughout the pregnancy, to matched controls. There were no significant differences between the groups. It was concluded that 6-MP therapy either before conception or after conception and during pregnancy was not associated with prematurity, spontaneous abortion, congenital abnormalities, neonatal and childhood infections or neoplasia. These more recent data support the conclusion that 6-MP is safe when used during pregnancy (55).

Nevertheless, a study at Lenox Hill Hospital found that pregnant patients treated in their first trimester with 6-MP had an increased risk of spontaneous abortions, and (in 2 cases) chromosomal abnormalities (mosaicism and trisomy 22) found at amniocentesis, leading to therapeutic abortion (56). Furthermore a study of men with IBD treated with 6-MP, whose wives became pregnant, showed a significant increase in congenital anomalies in the offspring when the father was taking 6-MP during the 3 months before impregnation (57).

Cyclosporine

The marked difference between cyclosporine and 6-MP or azathioprine in the treatment of inflammatory bowel disease is that a favorable response, when seen, is more apt to be seen earlier after administration of the former drug, usually within 1–2 weeks rather than the 3–4 months for the latter drugs. Cyclosporine acts on T rather than B lymphocytes and inhibits their proliferation. The rapid onset of action is due to inhibiting the production of interleukin-2 and the consequent release of multiple cytokines.

The first controlled trial of oral cyclosporine (using 5–7 mg/kg/day) in patients chronically ill with Crohn's disease, performed by Brynskov et al. (58), showed a statistically significant response rate of 59%, but coincidentally, a 31% response for placebo. A subsequent controlled trial failed to confirm this response in chronically active patients, although lower doses were used (59). Another controlled trial showed no difference in relapse rate with cyclosporine as compared to placebo, using low doses of cyclosporine (less than 5 mg/kg/day) (60). A new 12-month study (61) has been reported by European investigators using 5 mg/kg/day, and no major difference has been found when comparing cyclosporine plus low-dose steroids versus low-dose steroids alone.

At Mount Sinai, Present and Lichtiger used intravenous cyclosporine to treat Crohn's disease

(62). At an intravenous dose of 4 mg/kg/day for 14 days, which was then followed by oral doses of 6–8 mg/kg/day, a favorable response rate was noted in 88% of the patients. Closure of Crohn's disease fistulas occurred in 44% of these patients and improvement was noted in another 44%. Two-thirds maintained improvement in the chronic phase, and steroids could be discontinued in 75%. Hanauer and Smith (63) showed a similar response rate using this technique. Thus, oral cyclosporine seems to be less effective than intravenous cyclosporine, which may be due to malabsorption of the drug and/or the need for higher doses in inflammatory bowel disease patients with IBD.

The most promising data on cyclosporine comes from another study by Present and Lichtiger (64), who treated patients with ulcerative colitis via the intravenous route at 4 mg/kg/day for 14 days after a 7 to 10-day trial of parenteral steroids had been unsuccessful. A mean response time of 6.4 days was observed, and colectomy was avoided in 75%. A subsequent controlled trial has confirmed the efficacy of intravenous cyclosporine under these circumstances (65). Further observation has shown that oral cyclosporine has been successful for 6 months in 69% (66). This major long-term difference between the response in Crohn's disease and in ulcerative colitis might be attributed to the malabsorption so prevalent in the former and not in the latter. Also, the oral doses used in the Crohn's disease trial are far below the comparable IV dose. It is of interest that more than one-third of the patients entered into the controlled trial were referred by the surgical colleagues of Drs. Present, Gelernt and Bauer. The collegial relationship between our surgeons and gastroenterologists has encouraged many IBD advances at Mount Sinai.

Toxicity is of great concern when using cyclosporine, particularly intravenously. The foremost concern is nephrotoxicity. Fortunately, this toxicity can be minimized by carefully monitoring the blood urea nitrogen (BUN) and creatinine, keeping the cyclosporine blood level in a therapeutic range, and avoiding nonsteroidal anti-inflammatory agents and other drugs which may enhance the levels of cyclosporine and its toxicity. The risk of lymphoma and carcinoma is of concern, but in view of the doses and duration used for the treatment of IBD, cyclosporine has not been contraindicated. Other complications, such as tremors, hirsutism, gingival hyperplasia, paresthesia, headaches, and hypertension, although common, are almost always transient.

Intravenous administration of cyclosporine in the management and treatment of very sick patients with ulcerative colitis, in whom treatment with intravenous steroids has failed, is justified. The major risk in using intravenous cyclosporine when intravenous steroids have failed is waiting too long. Although the waiting period probably should be no longer than 7–12 days, some patients are already too ill to wait even that long for any hoped-for response to cyclosporine. Patients who are that ill are vulnerable to pneumonia, sepsis, and death, when they might have been saved by a timely colectomy. On the other hand, the risk of pneumocystis has been markedly reduced in some patients by the concurrent use of Bactrim (sulfamethoxazole-trimethoprim). In addition, should there be time for a trial of intravenous cyclosporine, its success will allow for introduction of the slow-acting immunosuppressive drugs 6-MP and AZA, which may then maintain remission for many years thereafter. This decision, of course, has to be based on a finely attuned clinical evaluation of the individual patient.

Although patients who respond to intravenous cyclosporine have continued with oral cyclosporine as well, the results on maintaining remission have been disappointing, presumably due to poor absorption, even with the advent of a newer preparation (Neoral) which has been shown to be better absorbed than the original drug (67). Consideration of the use of cyclospirne has been discussed by us elsewhere (67–69).

Anti-Tumor Necrosis Factor (anti-TNF) Alpha (Infliximab, Remicade)

In a short-term, multicenter study (including Mount Sinai), using a chimeric monoclonal antibody to tumor necrosis factor, 65% of patients with Crohn's disease improved vs. 17% on placebo, including 33% of the patients on anti-TNF in clinical remission after a single 2-hour infusion, with a better response after a lower dose of 5 mg/kg than after 10 mg/kg and 20 mg/kg (70).

Subsequently, Present et al. (71) used 3 infusions of anti-TNF to treat Crohn's disease fistulas, and demonstrated at least 50% healing in 62% of patients but in only 26% of patients on placebo ($p = 0.002$). Most recently, the results of a third multicenter study by Rutgeerts et al. (including DHP) (72) best documented the rates of relapse following the 3 infusions and recommended that the infusion be repeated every 8 weeks to maintain the remission. The reported toxicity so far has not been greater than that seen with 6-MP and AZA, but the development of anti-chimeric antibodies and hypersensitivity reactions after later infusions have been reported. No data is thus far available regarding the long-term potential for neoplasm.

The Present and the Future

Of all the immunosuppressive drugs now available, 6-MP and azathioprine have had the most enduring role and continue to show the most promise for the future. Despite the disadvantage of its slower onset, 6-MP has been consistently effective in two-thirds of patients with otherwise refractory Crohn's disease and those with ulcerative colitis. Azathioprine has also been effective for the same groups of patients. Because 6-MP is a metabolic byproduct of azathioprine, presumably weight-for-weight, the favorable effect of azathioprine is not as great as that of 6-MP. Nevertheless, this has never been submitted to any controlled trial. What is more important is the answer to the question as to why favorable results of treatment are consistently about two-thirds in patients with IBD. Why is it not 100%? What accounts for the other one-third? Perhaps the answer in Crohn's disease lies with the underlying pathology, particularly of the small bowel, in which repeated attacks of inflammation result in fibrosis which to date has been irreversible. After all, success with 6-MP in preventing small bowel obstruction has been consistently less than for other indications, such as elimination of steroids and closure of fistulas. A role for 6-MP in prevention of recurrence after bowel resection for Crohn's disease has now been confirmed (73), and it is now our practice to start 6-MP in the perioperative period.

Perhaps the answer lies in the role of inducing leukopenia with 6-MP or azathioprine. In retrospect, those patients who did develop leukopenia had greater success than those who did not (74). Furthermore, the successes came earlier and lasted longer, and those who did develop leukopenia had no clinical bone marrow depression. This can be attributed in part to what we have learned about careful monitoring. Our approach is to perform complete blood counts weekly for the first 3–4 weeks, and then if the white blood count does not fall and clinically there is no indication for increasing the dose of 6-MP, the time between blood counts can be extended. If, however, at any time, the symptoms recur and the white blood count permits, the dose of 6-MP should be raised. At this point, monitoring should be done weekly for 3 weeks. Another time for particularly careful monitoring is when steroids have been reduced or are about to be eliminated. Because the steroids had served to raise the white blood count, this stimulus may be lost and the patient may be vulnerable. In all cases, the patient must call after the blood count to receive new directions as to dose and when the next count should be done. Platelets also should be counted, because thrombocytopenia is sometimes seen during 6-MP therapy.

Another question is why leukopenia develops so easily in one patient but not in another. Although some patients tolerate as much as 200 mg a day without apparent effect on the white blood count, others tolerate only tiny doses such as 12.5 mg per week, or even less. This has been attributed to the absence or low levels of the enzyme thiopurine methyltransferase, which results in loss of catalytic activity. While the resulting leukopenia may lead to a rapid clinical response of IBD, the risks of bone marrow depression and allergic complications are proportionately increased (75, 76). This has led to the measurement of 6-thioguanine metabolites in an attempt to predetermine both the efficacy of the drug and its potential toxicity (77).

When leukopenia is first recognized in these patients, they have almost improved more than those without leukopenia, but when the dose has to be reduced further and further, the value of leukopenia is replaced by loss of overall drug efficacy.

The role of anti-TNF is being clarified very rapidly. Whether repeated infusions will maintain remissions of Crohn's disease on their own, supplement the maintenance role of 6-MP or AZA (or vice versa), or serve to effect earlier remissions then better maintained by 6-MP/AZA, is yet to be determined. Furthermore it must be clarified whether the temporary remission for sick hospitalized patients with Crohn's disease is better accomplished by intravenous steroids or Remicade, since the success rate for IV steroids is 88% within 10 days (78). Data comparing long-term steroid and Remicade toxicity might play a major role in deciding which drug should be used to initiate remission.

Other Immunosuppressive Drugs for IBD

Methotrexate has been effective for Crohn's disease, just as it has been for rheumatoid arthritis, but the toxicity profile has been greater than that of 6-MP/AZA and the maintenance less enduring. It has been reserved for patients who fail or are intolerant to 6-MP/AZA (79). Recent studies have shown that the combination of Remicade and methotrexate is very effective in rheumatoid arthritis patients. Future studies in Crohn's disease are required to see whether Remicade plus 6-MP or azathioprine is more effective than Remicade plus methotrexate.

The role of tacrolimus (FK506) has not yet been adequately tested (80). A controlled trial is currently underway using the newly formed Crohn's and Colitis Foundation of America Clinical Alliance. Other immunosuppressive drugs, including IL-10, IL-11, mycophenolate mofetil, and ICAM-1 (an anti-sense oligonucleotide) are being tried. Thalidomide has reappeared and has proved to have anti-TNF activity; since this drug can be given orally, it has already shown promise for treating Crohn's disease (81, 82).

Conclusion

Physicians at Mount Sinai and those who have trained there have played a major role in describing the clinical spectrum of inflammatory bowel disease. The opportunity to see and treat many of these patients has provided the experience to evaluate the many therapeutic innovations including the current use of immunosuppressive drugs. This evaluation is not yet completed, nor do we anticipate that treatments will be perfected until a better understanding of the pathogenesis of the disease has been achieved. The continuing clinical experiences at Mount Sinai and other institutions and the collaborative efforts of clinical and research scientists should help to attain the goal either of limiting the pain and suffering imposed by this disease or of eradicating it.

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Cancer in Inflammatory Bowel Disease

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Abstract

The first case of cancer in inflammatory bowel disease (IBD) was reported at The Mount Sinai Hospital in 1925 in a patient with ulcerative colitis (UC). In 1956, carcinoma of the jejunum was described in a patient with regional enteritis (Crohn's disease [CD]). IBD cancers are preceded by dysplasia, and the relative risk increases with duration of the IBD. CD cancers are more proximally distributed than are UC cancers. Both tend to occur at the site of the overt disease and both develop at earlier ages (47 UC, 50 CD) than in the *de novo* colorectal cancer (70 years).

The absolute cumulative colon cancer frequencies (8% UC, 7% CD) are identical after 20 years, emphasizing the importance of regular surveillance in both types of IBD. Moreover, the increased risk of colon cancer exists in patients with CD even when CD is confined to the small bowel, and patients with IBD have increased risks of developing extraintestinal and reticuloendothelial tumors in both CD and UC, as well as ano-vulval and malignant melanoma in CD. Colitic colorectal cancers are often diffuse, extensive, multiple and right-sided with insidious presentation. The prognosis is no worse after operation than that of *de novo* colon cancer.

Most small bowel cancers in CD are adenocarcinomas, rather than sarcomas, and present at a younger age, more diffusely and more distally than *de novo* cancers, usually making them undiagnosable at a curable early stage; indeed, two-thirds present with intestinal obstruction. Strictures of the colon are common in patients with IBD, and they have a 10-fold risk for colon cancer, 30-fold for UC, and 6-fold for CD. The risk increases with disease duration. The indications for surgery are absolute, relative and incidental, and the procedures include segmental resection, total proctocolectomy, subtotal colectomy and palliative procedures.

Key Words: Inflammatory bowel disease, cancer.

> We observed in one case a malignant degeneration of the late stage of polypoid ulcerative colitis, with the frank occurrence of carcinoma of the rectal wall. In brief this was a case of nonspecific ulcerative colitis of the colon 14 years in duration. The polypoid stage was already in evidence 10 years ago. More recently the patient came under observation with renewed symptoms of his disease. The sigmoidoscopic examination revealed an extensive polypoid colitis, in addition to which one observed on the left lateral wall of the rectal ampulla, growing in a mass of polypoid excrescences, an ulcerating massive neoplasm. Section removed for histological examination revealed the presence of an adenocarcinoma. (1)

Historical Background

For more than 70 years, surgeons and gastroenterologists at The Mount Sinai Hospital have been intrigued by the association of cancer with inflammatory bowel disease. Although Crohn is known for his description of regional ileitis, the first case of cancer in inflammatory bowel disease reported and described was actually one of ulcerative colitis-associated rectal cancer (see above) by Crohn and Rosenberg in 1925 (1). This was 66 years after the classic description of ulcerative colitis by Sir Samuel Wilks in 1859 (2). Since then, many reports have appeared confirming the high incidence of cancer of the large bowel in cases of ulcerative colitis, particularly for those with longstanding universal disease (3–5). The occurrence and significance of cancer in Crohn's

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disease were not appreciated until many years after the classic description of regional enteritis by Crohn, Ginzburg, and Oppenheimer was published in 1932 (6). Carcinoma occurring in association with Crohn's disease was first recognized in the large bowel (7), then in the small bowel (8) (see below), and subsequently at extraintestinal locations (9).

Dr. Leon Ginzburg et al. described a case of "carcinoma of the jejunum occurring in a case of regional enteritis" in 1956 (8):

> This was believed to be the first report of carcinoma arising in the small intestine at the site of stenosing granulomatous enteritis. From the age of 11 until 30 this patient had been subjected to frequent bouts of crampy abdominal pain, with marked but non-bloody diarrhea, followed by relative constipation. In October of 1952 a gastrointestinal series revealed rigidity of the segments of small bowel involving the jejunum, with areas of dilatation between. A diagnosis of ileojejunitis was made. He was admitted with acute intestinal obstruction. Physical examination revealed a thin patient with distended abdomen and visible peristalsis, and hyperactive peristaltic rushes on auscultation. The entire segment from 18" to 6 feet from the ligament of Treitz, with multiple strictures, was resected. The tumor mass 40 cms from the proximal end consisted of an adenocarcinoma arising from the mucosa and invading the bowel wall. Cords of anaplastic cells invaded the serosa. Seven months later the patient was readmitted with widespread metastatic disease also involving the liver.

This case report describes a typical case of carcinoma occurring in stricturing small bowel disease. We have seen patients with cancer-complicating stricturing disease.

For several decades following the early description of granulomatous disease of the bowel by Dalziel in 1913 (10) and its fuller elucidation by Crohn, Ginzburg, and Oppenheimer in 1932 (6), it was generally accepted that cancer did not occur with Crohn's disease. There were no reports of cancer until 1948, when Warren and Sommers described the first case of carcinoma of the large bowel occurring in association with Crohn's disease (7). The number of described cases has increased dramatically over the last few decades. There are now considerably more than 128 patients in whom cancer of the large bowel has been reported in association with Crohn's colitis, ileocolitis, and even regional enteritis (11).

The first reports of cancer occurring in the jejunum in patients with regional ileitis and jejunitis were those of Ginzburg et al. (8) and Kornfeld, Ginzburg and Adlersberg (12). These authors described the following case.

> A 36-year-old white woman was admitted to The Mount Sinai Hospital in 1955. She was suffering from upper abdominal pain, persistent vomiting, loss of weight and marked weakness. Her initial gastrointestinal symptoms, characterized mainly by severe diarrhea, were first manifested eight years previously. At that time she was admitted to another institution where radiological studies revealed evidence of colitis. She continued to have four or five watery bowel movements daily which never showed evidence of blood pus or unusual quantities of mucus. Her weight fell from 125 to 75 pounds. She was treated by one of us with Aureomycin and cortisone and regained 40 pounds in weight in a few months. Despite radiologically demonstrable widespread disease she remained actively employed for five years. An obstructive episode was treated by suction and followed by four months of medical treatment. Radiologic studies revealed dilated jejunum and a rigid segment. She was readmitted with obstruction and found to have an unresectable jejunal mass and multiple areas of disease. She died with metastatic liver disease six months after a retrocolic duodenojejunal bypass.

Since this time, more than 80 cases of cancer of the small bowel have been reported in patients with Crohn's disease (13 – 15). Among these cases, 17 have occurred in excluded segments of bowel (13, 16 – 18), of which 7 cases have been reported from this hospital (Fig. 1) (19).

Brown, Weinstein and Janowitz (16) described a "carcinoma of the ileum 25 years after bypass for regional enteritis" in 1970. This 55-year-old woman was admitted to The Mount Sinai Hospital in 1969. Twenty-five years earlier, she had developed low abdominal pain and fever. At laparotomy 6 months later, Crohn's ileitis was found and an ileotransverse colostomy was constructed. Because of obstruction, this was revised to a side-to-side ileodescending colostomy (see Fig. 1, case 3 RC), leaving the proximal colon in place. At re-exploration, the terminal ileum and cecum were resected and an adenocarcinoma with two positive lymph

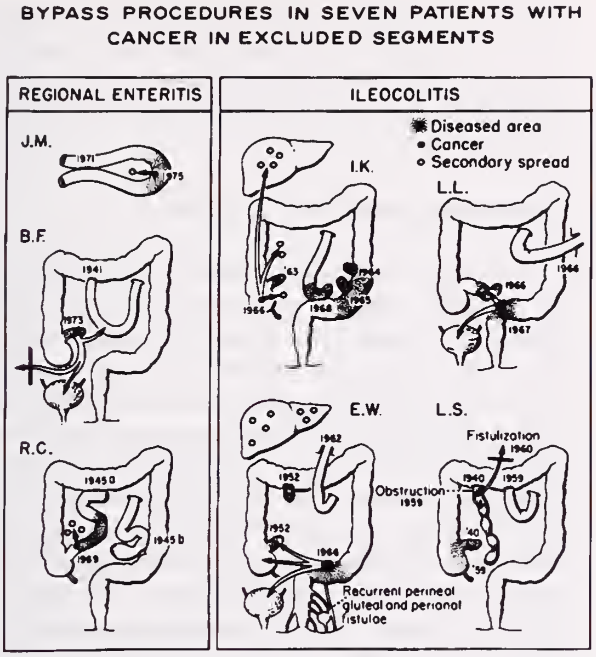

Fig. 1. Bypass procedures in seven patients with cancer in excluded segments.

JM = metastasizing cancer in jejunum four years after side-to-side jejunoileal bypass in-continuity.
BF = fistulizing cancer in terminal ileum thirty-three years after ileotransverse colostomy with exclusion.
RC = locally metastasizing cancer in terminal ileum twenty-five years after ileodescending colostomy with exclusion.
IK = metastasizing cancer in uninvolved cecum four years after diverting ileostomy and subsequent ileosigmoid bypass of terminal ileum.
LL = fistulizing cancer in diseased sigmoid colon two years after diverting ileostomy.
EW = fistulizing metastatic mixed mesodermal sarcoma in diseased sigmoid colon fourteen years after exclusion bypass of terminal ileum and four years after diverting ileostomy.
LS = cancer in multiply strictured segment of ileum, occurring at site of nineteen-year-old ileotransverse colostomy, and discovered upon malignant fistulization after secondary bypass.

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nodes was found. She developed a subphrenic abscess and died on the 31st postoperative day.

General Considerations

It is generally accepted that the numbers of cases of inflammatory bowel disease (IBD)-associated cancer in the colon in ulcerative colitis (UC) and in the small bowel in Crohn's disease (CD) have increased. The question of the colorectal cancer (CRC) risk in Crohn's disease remains controversial and will be discussed in detail below. Early reports suggested a poor prognosis for all gastrointestinal cancers in inflammatory bowel disease, but recent studies of larger series of patients have indicated a better prognosis, especially in patients with colitic colorectal cancer. In these patients, survival is similar to that in non-colitic CRC.

Clinico-Pathologic Features of IBD Cancer

Cancers occurring in IBD differ in many respects from those occurring *de novo*. In general, they occur earlier in life; the anatomic distribution is different, being influenced by sites of disease; and they are more frequently multiple and mucinous. The cancer risk is greater than in the general population (Fig. 2), and increases with longer disease duration (Fig. 3). In both diseases, cancer is preceded by dysplasia, which allows for surveillance for colorectal cancers. Both ulcerative colitis CRC (UCCRC) and Crohn's disease colorectal cancer (CDCRC) occur in association with strictures, although UC strictures are more frequently malignant.

Cancers occurring in CD, although similar in many respects, differ in some respects from those developing in UC. CD cancers have a more proximal distribution; may occur throughout the gastrointestinal tract, since CD is a diffuse disease; and may occur in association with fistulas or excluded loops. In both diseases, cancers tend to occur at sites of overt disease. In CDCRC, cancers may occur in normal-appearing bowel in as many as one-third of patients (20). We have recently described six patients (a seventh has been seen more recently) with Crohn's disease limited to the small bowel, who developed cancers of the colon and rectum (21). These observations of a wide distribution of cancer within the intestinal tract, as well as the occurrence of diffusely infiltrating (22) and multiple (23) cancers, are consistent with the fact that Crohn's disease may affect the whole gastrointestinal tract, even in the absence of overt disease (24–27). Furthermore, recent endoscopic studies have shown that one-third of patients with Crohn's disease, and even some patients incorrectly diagnosed as having ulcerative colitis, have macroscopic or histologic evidence of involvement of the upper gastrointestinal tract in the absence of any radiologic changes (28). Each of the above features of cancer in CD will be considered in detail below.

Cancer Risk

Overall Risk

Several studies have suggested an increased incidence of gastrointestinal cancer in patients

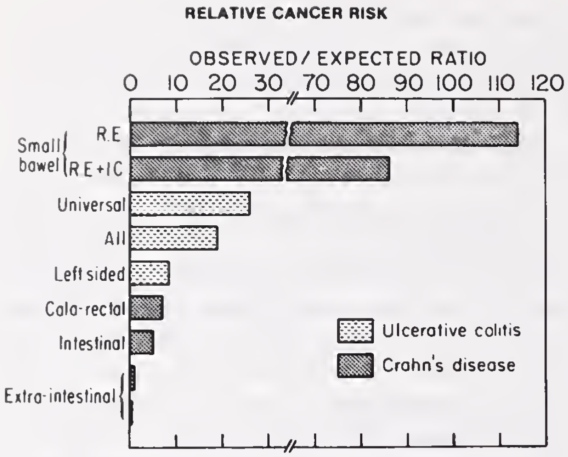


Fig. 2. Relative cancer risk in patients with ulcerative colitis and Crohn's disease.

R.E. = Regional Enteritis.

I.C. = Ileocolitis.

Universal = universal colitis involving all segments of colon and rectum.

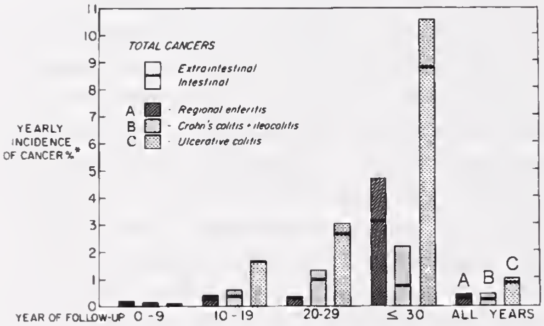


Fig. 3. Incidence of gastrointestinal cancer in Crohn's disease and ulcerative colitis for patient years at risk starting from onset of first symptoms. The cancer risk increases progressively with each passing decade for all categories of inflammatory bowel disease, but the absolute incidence rates are three times higher in ulcerative colitis than in Crohn's disease.

Bars:

A = Regional enteritis — left bars

B = Crohn's colitis + ileocolitis — middle bars

C = Ulcerative colitis — right bars

For each decade of follow up, Extraintestinal yearly incidence, in percent, is indicated by the amount above the horizontal line within each bar, while the yearly incidence, in percent, for Intestinal cancer is indicated below the horizontal line.

with Crohn's disease. Fielding et al., in 1972, found seven cancers in the gastrointestinal tract, including two in the pancreas and two in the small bowel (29). Alexander-Williams' 1976 series of 12 gastrointestinal cancers among 500 patients with Crohn's disease also included higher than expected numbers of cancers in small bowel, large bowel, esophagus, and pancreas (30). Similarly, our 1979 study of Mount Sinai patients revealed an increased incidence of both small and large bowel cancers when compared with an age- and sex-matched population (Fig. 3) (5). The incidence of gastrointestinal cancer in Crohn's disease increased with disease duration in a way similar to that in ulcerative colitis (Fig. 3) (14).

Colorectal Cancer Risk in Colitis

The risk of colorectal cancer is considerably increased for patients with ulcerative colitis, particularly for those with universal disease (all segments of colon and rectum) of long standing (7–9, 31). The overall incidences of ulcerative colitis-associated colorectal cancers (fewer than 1,000 per year in the United States) and of Crohn's colitis (less than 100 per year) are not high when compared with the total yearly incidence of 140,000 for colorectal cancers in the general population. Nevertheless, the issue of colorectal cancer risk in inflammatory bowel disease must take into account a number of important factors. First, the relative risk of colorectal cancer is much increased in age- and sex-matched populations in both ulcerative colitis and Crohn's colitis. Second, both forms of colitis colorectal cancer occur in patients younger than in *de novo* colorectal cancer. The mean age at development of cancer is approximately 56 years for Crohn's colitis and 49 years for ulcerative colitis, compared with 70 for *de novo* colorectal cancer (32). Third, since colitis colorectal cancer is a premalignant condition, cancer could theoretically be prevented in both UCCRC and CDCRC if high-risk cases could be identified early, so that timely colectomy could be carried out.

There is much controversy regarding the incidence of colorectal carcinoma with Crohn's disease. A high incidence was reported in two early publications from England. In 1965, Atwell et al. in Leeds reported three colorectal cancers among 62 patients, an incidence of 5% (33). Then, in 1968, Perrett et al. in Oxford found three cases among 82 patients with Crohn's disease, a 4% incidence (34). Although other series failed to confirm as high an incidence, Weedon et al. at the Mayo Clinic found that their patients with Crohn's colitis, whose disease onset occurred before 21 years of age, had an incidence of colorectal cancer 20 times higher than expected (35). The seven colorectal cancers in our early series of 327 patients (2%) with Crohn's colitis or ileocolitis represented an increased incidence of about 7 times what was expected (14). We now have a collected series of 30 (3 multiple) colorectal cancers among our patients with Crohn's disease. Eight large bowel cancers occurred in seven patients with regional enteritis and 25 among 23 patients with colitis and ileocolitis.

Warren and Sommers reported the first case of adenocarcinoma complicating Crohn's disease in 1948 (7). For the next 30 years, reports of single (22, 36), and even multiple cases (23, 33, 35–38), failed to dispel the skepticism surrounding this association. More recent studies, however, have clearly demonstrated the increased risk of colorectal cancer for those patients with Crohn's disease who have extensive, longstanding, unresected colonic involvement (14, 20, 39, 40). Nevertheless, the association between Crohn's disease and colorectal cancer remains controversial, with a number of doctors disputing the association (41–45). However, each of these five populations-based studies calculated their relative risks without specific regard to the population actually at risk; namely, patients with "extensive, longstanding, unresected" colonic disease. All of these studies show an increase in relative risk of approximately 10-fold if corrected for these factors (46). A recent study from Birmingham compared the cancer risk between two hospital-referred but identically selected cohorts of patients with extensive ulcerative colitis and equally extensive Crohn's colitis (40). This study established a virtually-identical, absolute, cumulative frequency of 7% and 8%, for CD and UC respectively, at 20 years, thereby confirming the previously noted similarities between cancer incidences in these two diseases (14, 20, 39). In their prior 1994 study (47), Gillen et al. found that the relative risk of 4.9 for colorectal cancer increased to 13.3 for patients younger than 25 years of age at onset of CD, and to 18.2 if corrected for extensive colitis. If both factors were present, the risk rose to 57.2. Thus, in the presence of longstanding, extensive disease and unresected colon (this would seem to be obvious, but many authors have failed to exclude patients who have "no colon" and therefore are at "no risk!"), especially with early onset of Crohn's disease, the risk clearly is increased. In these high risk patients, it could be argued that as in ulcerative colitis regular surveillance should be carried out.

Colorectal Cancer Risk in Regional Enteritis

One question that remains unresolved is the possible association between colorectal carcinoma and small bowel Crohn's disease (42, 48). Even though seven (23%) of our patients, five of whom were previously reported (15, 21), had overt Crohn's disease confined to the small bowel, they nonetheless developed eight carcinomas. Five of these occurred in the colon and three in the rectum. It could be argued that colorectal cancer, being a common disease, appeared only coincidentally in two patients, both of whom were more than 60 years of age, with short duration disease at the time of cancer diagnosis. However, three of the seven ileitis cases presented with colorectal cancers, at ages 34, 38, and 42, suggesting a true increase in risk, and two developed cancer after 30 and 31 years of disease, at ages 70 and 78 respectively. Moreover, there were no significant differences in age at onset of Crohn's disease, age at cancer, and duration of disease to cancer, between patients with ileitis and those with either ileocolitis or colitis. This finding once again raises the question of whether small bowel Crohn's disease even predisposes someone to colorectal adenocarcinoma (42, 48), which would be consistent with the panenteric nature of this disease.

Extraintestinal Cancer Risk

Although several studies prior to 1983 failed to demonstrate a statistically significant increase in incidence for extraintestinal cancers in patients with inflammatory bowel disease (14, 20, 38, 49), a more recent study of 2,000 patients with inflammatory bowel disease has shown an increase in three specific tumor groups in patients with either Crohn's disease or ulcerative colitis (4). The first group includes reticuloendothelial tumors: leukemias in ulcerative colitis (50, 51) and lymphomas in both ulcerative colitis and Crohn's disease (4, 52). The second group comprises tumors arising from chronic perineal inflammation in Crohn's disease: squamous carcinomas of the anus and vulva (4, 53). Finally, there may be an increased incidence of malignant melanoma in Crohn's disease (4, 54). It remains to be seen whether an increased risk of any of these cancers, some of which are similar to the types that occur in immunosuppressed and/or irradiated patients (55), can be documented in other medical centers.

Colorectal Cancer

Clinicopathological Features: Colitic colorectal cancers show characteristic clinico-pathological features that tend to distinguish them from other colorectal cancers. They are more diffuse, not infrequently extending over more than one segment of bowel. They may be invisible to the naked eye, or they may infiltrate the bowel wall causing stricture formation. They are frequently multiple, and the incidence of right-sided cancer is greater in colitis-associated than in *de novo* colorectal cancer, due largely to right-sided disease in CD and to the increased incidence of multiple synchronous cancers (32).

Cancers in colitis and regional enteritis have the unfortunate tendency of developing without giving clinical evidence of their presence in their early stages. Advanced cases are characterized by obstructive symptoms, rapid weight loss, and abdominal masses. Colorectal cancers in Crohn's disease may occur in excluded distal bowel or in association with enterovesical or colovesical (Fig. 1) (19, 56), rectovaginal (57, 58), colocutaneous (19, 59), or perianal fistulas (19, 53, 60). Crohn's disease colorectal cancers share some features with ulcerative colitis colorectal cancers. The clinicopathological features of colorectal cancer occurring in Crohn's disease, as in UC, are difficult to differentiate from the clinical features of the underlying inflammatory bowel disease. Compared to *de novo* cases, colorectal cancers in Crohn's disease occur at an earlier age (48 vs. 70 years), are more often located in the right colon (45%), and are more frequently multiple (22, 23). Multiplicity is less of a feature than in UCCRC where the incidence of multiplicity is reported to be 14–40%, compared with 4% for *de novo* colorectal cancer (32). It has been suggested that there are two separate populations among these patients. First, there are those with onset of Crohn's disease at older than 60 years of age, in whom the vast majority have had a relatively short duration of disease and in whom the Crohn's disease and cancer symptoms occurred simultaneously. This group, for example, constitutes approximately 20% of the patients in Hamilton's series (61). The second and much larger group consists of younger patients, usually with a long duration of disease. Examination of the literature prior to 1985 reveals that for all 29 patients younger than 60 years of age, for whom the duration of disease is recorded, the mean disease duration was 15 years, while for the 29 patients older than 60 years of age, the mean disease duration was 5 years. This thesis regarding two populations has been supported by a recent publication by Kyle and Ewen, who describe two such separate populations among patients in their area who developed Crohn's colorectal carcinoma (62). However, in Hamilton's series, there are also three older patients with long disease durations of 36–51 years, suggesting a third group with both older onset age and longer pre-existing disease duration (61). Six patients with onset of the disease after 70 years of age had a mean disease duration of 25 years, but two elderly patients had simultaneous onsets of Crohn's disease and cancer at ages of 68 and 72, as first described by Hamilton (61). Since onset age of Crohn's disease in the sixth decade of life is unusual and the incidence of spontaneous colorectal cancer increased in late decades, patients in this latter group could represent either coincidental spontaneous cancer or colitis-associated cancers in a setting of longstanding, undiagnosed Crohn's disease.

Cancer of the Small Bowel

Clinicopathological Features: Most cancers of the small bowel in Crohn's disease are adenocarcinomas, usually in the terminal ileum or jejunum; they are difficult if not impossible to diagnose at a curable stage. They differ from *de novo* cancers of the small bowel in many respects (13, 63). There is a lower average age at diagnosis of cancer in Crohn's disease, 45 years vs. 60 years; the site of cancer is more distal, 76% vs. 20%; and the mean postoperative survival time is less, 8 months vs. 32 months. Furthermore, sarcoma is an extremely rare form of small bowel cancer in Crohn's disease, whereas approximately one-third of *de novo* small bowel cancers are of this variety. There is also an increase in the proportion of multifocal or diffuse cancers in association with Crohn's disease. As with ulcerative and Crohn's colitis, the incidence of cancer increases with longstanding duration of Crohn's disease (Fig. 3).

In our 18 patients with known sites of intestinal cancer, the mean duration of Crohn's disease was 22 years (18 years for cancers occurring in bowel in-continuity and 28 years for cancers occurring in excluded bowel) (19). Hoffman et al. have reported similar figures, with 90% of their cases lasting more than five years, 70% more than ten years, and 38% more than 20 years from the onset of disease, yielding a mean disease duration of 18 years (63). Although the majority of cancers of the small bowel occur after a long duration of disease, Fresco et al. have drawn attention to the fact that as many as one-third of all cases may occur within the first decade of disease (64). However, the total number of patients at risk in the early onset group is much greater than in subsequent decades; hence the true cancer risk is much lower.

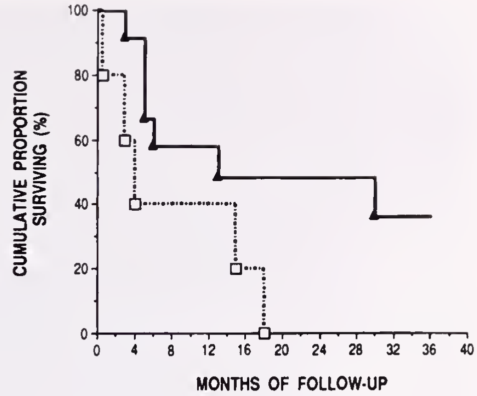
The most common clinical presentation of small bowel cancer is intestinal obstruction. This occurred in two-thirds of our patients (19). Other important symptoms include diarrhea, weight loss, abdominal mass, and abdominal fistulae (15, 37). These symptoms are also found in Crohn's disease without cancer. The possibility of the development of complicating cancer should be entertained if the development of these clinical features follows "a long quiescent period" (19). Small bowel cancer is rarely suspected preoperatively, the diagnosis being made in fewer than 5% of reported patients, and in only two of our nineteen. Intraoperative, postoperative and autopsy diagnoses were made in 27%, 61%, and 7% respectively, of those 44 patients reviewed by Hoffman et al., for whom the timing of the diagnosis could be determined (63).

Three key microscopic features were described by Fleming and Pollock: invisibility, mucosal dysplasia, and endometriosis-like invasion of the stroma (65). Invisibility is defined as microscopic recognition when the cancer is difficult to perceive, even on opening the operative specimen. Mucosal dysplasia, similar to that originally described by Morson and Pang in ulcerative colitis (66), is found in 25% or more of cases of CDCRC (65, 67, 68) and suggests that surveillance should be carried out in selected cases with Crohn's disease.

The prognosis of carcinoma of the small bowel in Crohn's disease is poor. Among the 44 patients reported by Hoffman et al. (63), there were only two 5-year survivors (5%), compared with the 20–30% 5-year survival rate for *de novo* small bowel cancers. The mean postoperative survival time in those Crohn's disease patients who survived surgery was only 7.8 months. All of the small bowel cancers initially reported by Greenstein et al. (14) were fatal. However, in a larger series reported more recently, although all of the five patients with cancer in excluded bowel died within 18 months, the overall survival rate at three years was 23% (Fig. 4) (15). The survival rate of more than 30% at three years for in-continuity cancer was similar to that for *de novo* small bowel cancer. The prognosis for large bowel cancers is better. With colonoscopy today, we can expect an increased and earlier preoperative detection of colorectal cancer in Crohn's disease, and thus possibly a better prognosis for the large bowel variety, but not for that in the small bowel. Small bowel enteroscopy and push enteroscopy can now be tried but there is no proof of their diagnostic value.

Strictures and Cancer

Enteric strictures are one of the common complications of Crohn's disease and are caused by marked thickening of the bowel secondary to intramural fibrotic change. The frequency of benign colorectal strictures in Crohn's disease, and the difficulty of differentiating them from malignant strictures (Figs. 5 A, B, C), makes this a topic of major importance in the attempt to diagnose cancers at an early and curable stage. Although strictures occur more frequently in the small intestine than in the colon, 5–17% of patients with colonic Crohn's disease have a colorectal stricture. One hundred thirty-two of 980 patients (13.5%) with CD involving the colon, admitted to The Mount Sinai Hospital between 1959 and 1985, developed 175 colonic strictures (69). Thirty-three patients developed more than one stricture. The frequency was twice as great in colitis (19%) as in ileo-colitis (11%). Ten malignant strictures were identified in 9 patients (3 ileocolitis, 6 colitis). One of these patients had three strictures (2 malignant and 1 benign), and two had 2 strictures (1 malignant and 1 benign).



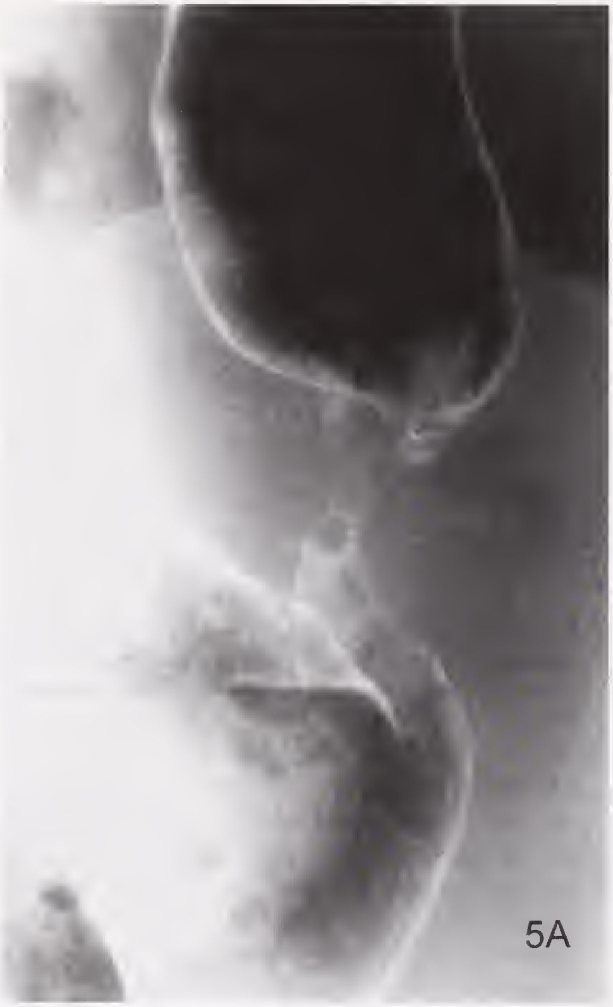
MONTHS OF FOLLOW-UP	0	0 5	3	4	5	6	13	15	18	30	36
▲ PATIENTS WITH CANCER IN-CONTINUITY	*0/14	0/14	1/12	0/11	3/11	1/8	1/6	0/5	0/5	1/4	0/2
□ PATIENTS WITH CANCER IN EXCLUDED BOWEL	0/5	1/5	1/4	1/3	0/2	0/2	0/2	1/2	1/1		

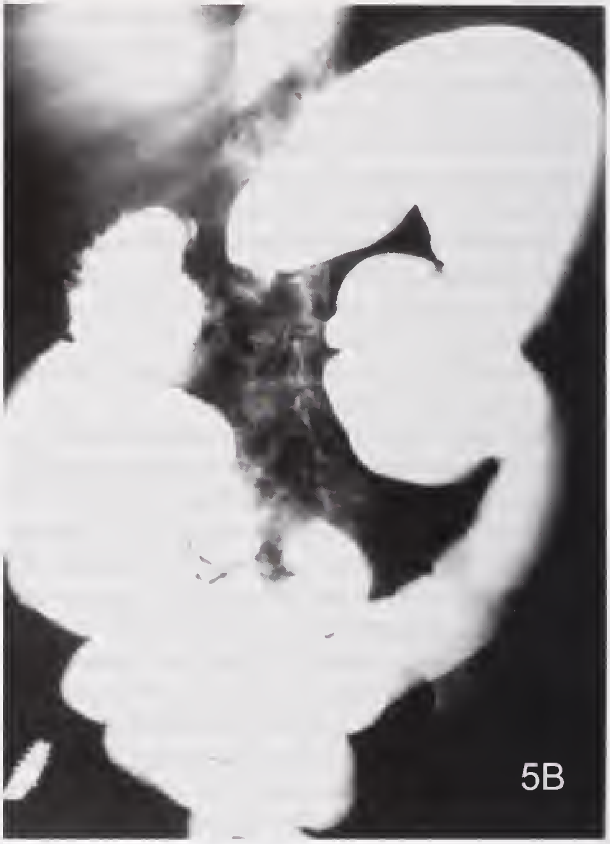
* NO OF DEATHS / NO OF PATIENTS AT RISK

Fig. 4. Survival curves for five patients with cancer in excluded bowel and 14 patients with cancer in non-excluded bowel. The difference did not reach statistical significance. Reprinted from reference #15 with permission.

The frequency of cancer in patients with stricture (6.8%) was higher than in those without stricture (0.7%, 6 of 848, $p < 0.001$). There were no differences in clinical symptoms between patients with benign and malignant stricture. Seventeen of 165 benign strictures (10.3%) were long, extending over more than one anatomical segment of colon, but all ten malignant strictures were short ($p < 0.0001$).

The age at the diagnosis of stricture was significantly higher in the 9 patients with malignant stricture than in the 123 patients with benign





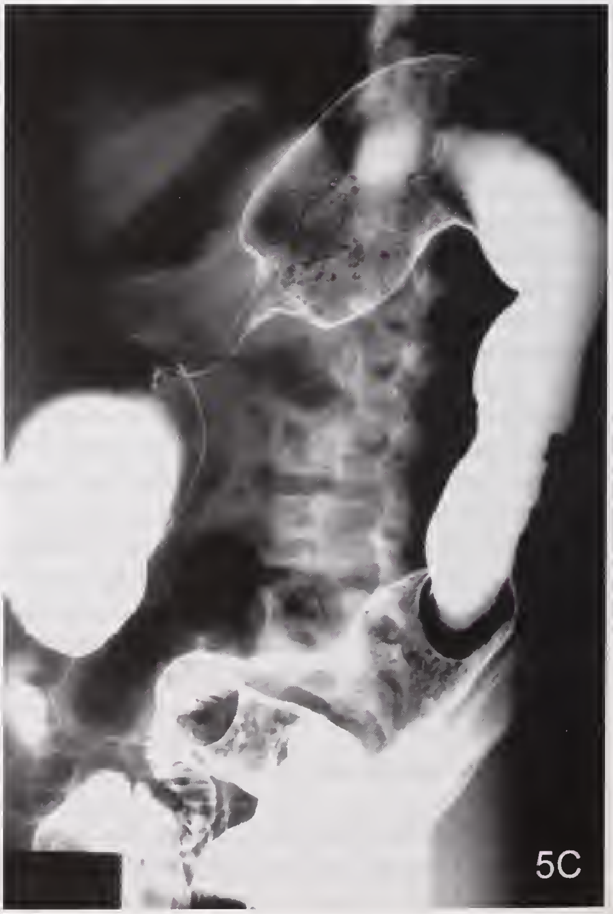


Fig. 5. Malignant and benign strictures in inflammatory bowel disease.

A. Malignant stricture in ulcerative colitis in which the cancer was missed for a year after endoscopy failed to pass the stricture.

B. Benign stricture in Crohn's disease in which malignancy was suspected.

C. Thirty-five-year-old woman who had Crohn's colitis for 20 years. She developed multiple colonic cancers. Only the malignant stricture of the transverse colon is readily apparent in this X-ray. She survived for five years following chemotherapy despite transmural metastases found at laparotomy.

stricture (mean age 57.2 vs. 41.4 years, respectively, $p < 0.01$). The proportion of strictures that were malignant increased with duration of disease, from 3.3% with less than 20 years of CD, to 11% with CD of 20 years or more. All nine patients with malignant stricture were treated surgically, and 4 of the 9 died of colon cancer during a mean follow up of 4.3 years. In view of the high rate of malignancy, 6.8%, in this series, colonoscopy with biopsy is essential in Crohn's disease patients with colonic strictures, and surgery is mandatory when a stricture cannot be fully assessed during colonoscopy. Unlike ulcerative colitis, in which proctocolectomy is required, in segmental Crohn's disease, a more limited segmental resection may be appropriate treatment in some patients. Follow-up surveillance is essential in these patients.

The frequency of colon cancer in stricture patients was 10 times higher than in non-stricture patients in our series. Although there appears to be an association between colorectal cancer and stricture, it is not clear whether benign strictures degenerate into malignancy or whether cancers present as strictures. The proportion of malignant strictures increased with increasing duration of Crohn's disease (Fig. 2). This observation is consistent with the fact that longer duration of disease is associated with increased risk of colorectal cancer, with or without stricture. Malignant disease must be ruled out if a stricture is found in a patient with Crohn's (ileo)colitis. Radiological examination is of value for detection of colonic stricture, but is not reliable for the differentiation of benign from malignant disease. Following radiological detection of a stricture, endoscopy with biopsies throughout of the length of the stricture is essential. Multiple biopsies should be taken at the proximal and distal edges, and from within the stricture, in order to rule out dysplasia, carcinoma *in situ*, or frank adenocarcinoma. Surgery must be considered whenever the endoscopist cannot visualize the entire length of the stricture.

As in Crohn's disease, any patient with ulcerative colitis who develops a stricture or obstruction should immediately be evaluated by colonoscopy. The risk of cancer is even greater in UC strictures. Gumaste et al. found that 17 of 58 patients with colorectal strictures in UC had malignant strictures (70). Seven of these 17 patients with malignant strictures in ulcerative colitis presented with partial or complete obstruction, compared with none of 42 with benign strictures. In both Crohn's disease and ulcerative colitis, a remarkable degree of narrowing, sometimes to as small as one to two millimeters, can occur without the development of obstructive symptoms, which must be attributed to the liquidity of the stool.

Surveillance of Crohn's Disease for Carcinoma

Surveillance for cancer in patients with Crohn's disease remains controversial, but should seriously be considered for selected groups of patients who are at a high risk for the development of colorectal cancer. In the 1980s, Korelitz (71, 72), and Shorter (73) suggested the need for surveillance, while Butt (74, 75), Fielding (29), and Warren (7) did not advise prophylactic measures, but they recommended "vigilance." In 1985, Hamilton (61) suggested that cost-benefit studies of surveillance protocols were needed in well-defined Crohn's disease populations.

Several factors make it difficult to propose a rational surveillance program for Crohn's disease patients. These factors include the variety of cancers which occur in association with Crohn's disease: extraintestinal (4) and intestinal (14), small bowel (3, 13, 15, 18. 64), and large bowel (2, 35, 61, 68). There are also several different modes of clinical presentation: cancers following long duration of disease (3), cancers coincident with onset of Crohn's disease (34, 37, 61, 67), cancers remote from overt disease (13, 14, 61, 76), and cancers in excluded segments (19). Finally, there are features that make the diagnosis difficult to establish even when a lesion is suspected and sought: the inaccessibility of small bowel to endoscopic examination, the difficulty of evaluating segments of bowel that are either bypassed (16, 18, 19, 77) or proximal to strictures (4, 69, 78), the "invisibility" (65) or "occult" (67) nature of the neoplasms, and the confounding of cancer symptoms with those of the underlying bowel disease.

I have proposed that regular clinical checkups should be instituted for patients with Crohn's disease, including examination of the abdomen and, because of extraintestinal cancers (see below), review of the reticuloendothelial system and skin, especially the anovaginal area. An explanation should be sought for recurrence of old symptoms or for development of new symptoms, particularly stricture, fistula, intestinal bleeding or weight loss, especially if these symptoms develop after a long period of quiescent disease. Excluded segments should be removed whenever re-operation is being performed. Patients with perianal abscesses, and internal and external fistulae should be considered to be at some risk for malignant transformation of these areas of chronic inflammation. A routine endoscopic surveillance program can be recommended for selected patients with longstanding (more the 10 years), universal disease, especially with early onset of CD. A controlled study should be designed to see if earlier diagnosis, leading to curative resection, could be made, utilizing multiple biopsies for dysplasia. In view of the occurrence of carcinoma in overtly normal appearing bowel, and in the colon and rectum in regional enteritis, biopsies of both normal and abnormal bowel would have to be made and examined for dysplasia, carcinoma *in situ*, and infiltrating carcinoma. Biopsies would also have to be taken from elevated masses, adenomatous polyps, and especially from areas of stricture and fistula formation. Prophylactic colectomy should be advised if dysplasia develops in the absence of acute inflammation, and especially if dysplasia is found in the presence of an elevated mass. It remains to be seen whether small bowel enteroscopy will enable differentiation of benign from malignant strictures in the more proximal bowel.

The ratio of costs and risks to benefits has not been established for prophylactic colonoscopic surveillance, nor has an optimal surveillance regimen been determined. On an empirical basis, most such programs commence after 10 years of disease, often on an annual or biannual schedule. One could argue for earlier surveillance in view of the relatively high incidence of cancers in Crohn's disease during the first decade. Newer and more sensitive indicators of premalignancy, such as DNA flow cytometry, cell turnover kinetics, mucin histochemistry, lectin binding, or monoclonal antibody identification of antigenic tumor markers, may ultimately supplant routine histologic examination for dysplasia as more effective screening techniques.

Indications for Surgery

A. Absolute

1. High-grade dysplasia or low-grade dysplasia found in patients in surveillance programs in the absence of acute inflammation, with or without a dysplasia-associated lesion or mass (DALM).
2. Carcinoma proven by endoscopic biopsy.
3. A stricture that cannot be passed.

B. Relative

1. An excluded loop; although patients often refuse surgery if quiescent.
2. A poorly compliant patient on whom regular surveillance cannot be done.
3. Surveillance is impossible in the high-risk patient because of multiple, large pseudopolyps or the difficulty of differentiating the dysplasia of adenomatous polyps.

C. Incidental

1. Patients may be operated on for other indications unrelated to the cancer, such as fulminating colitis, toxic megacolon or a cancer found pathologically.

Principles of Surgery for Colorectal Cancer in IBD

The surgery for cancer in IBD is based on the principles which have evolved for cancer surgery in general: wide excision with lymphadenectomy, which should be carried out in conjunction with appropriate surgery for the inflammatory bowel disease.

In Crohn's colitis, except when the disease is extensive or universal, or severe perianal disease is present, segmental resection (SR) with reanastomosis is an option and frequently the preferred method of treatment. Although there is a high recurrence rate for colocolostomy, ileo-sigmoidostomy or ileo-proctostomy, these more limited resections allow the patient to retain the rectum, maintain intestinal continuity, and avoid a permanent ileostomy for variable periods of time. This is especially valuable in young patients. In CD, ileoanal pouch construction is at this time contraindicated. In indeterminate colitis, pelvic pouch construction may be successful with results almost as good as for ulcerative colitis (79).

Between 1960 and 1989, a total of 147 patients with cancer occurring in IBD were seen at The Mount Sinai Hospital in New York City. There were 30 with large bowel adenocarcinoma in CD, compared with 102 patients with CRC in UC (80). An additional 19 patients were seen with small bowel cancer (SBC) (15). The four groups of surgical procedures required for these patients included segmental resection (SR), total proctocolectomy (TPC) with end ileostomy or pelvic pouch (in UC only), subtotal colectomy (STC) with or without reanastomosis, and various palliative procedures (PP) including diversionary colostomy or ileostomy. The surgical procedures in our 130 patients with CC and UC complicated by CRC are listed in Table 1.

Segmental Resection (SR)

Segmental resection, right, left or distal abdominoperineal, was the preferred surgical therapy for Crohn's colorectal cancer, cancer occurring in what was often a segmental disease (Table 1). In this series, seven cases of colorectal cancer occurred in patients with regional enteritis localized to the small bowel (21). These cases were clearly ideal for SR, which was carried out in 14 patients, 46% of the series.

Total Proctocolectomy (TPC)

In CD, TPC is generally reserved for those patients with extensive or universal colitis, espe-

TABLE 1
Surgical Procedures for Colorectal Cancer in Inflammatory Bowel Disease

	Ulcerative Colitis			Crohn's Disease		
	Subtotal	Procedure		Subtotal	Procedure	
	n	n	%	n	n	%
Total Proctocolectomy	51			5		
with ileostomy		43	43		5	17
with pelvic pouch		8	8		0	0
Subtotal Colectomy	25			5		
with ileostomy		11	11		4	14
with reanastomosis		14	14		1	3
Segmental Resection	14			14		
ileocolic		0	0		2	6
right colectomy		7	24		1	3
left colectomy		1	0		4	14
sigmoid/ant. res.		1	1		1	3
protect/Hartmann		0	0		1	3
abdomino-perineal		5	5		5	16
Palliative Procedure	5			5		
ileostomy		1	1		3	10*
colostomy/Hartmann	4	4**		2	7	
Unresectable						
inoperable/biopsy	4	4	4	1	1	3
laparotomy	1	1	1	0	0	0
TOTAL	100		100	30		100

* One with proximal jejunojejunostomy and ileoileostomy.
** One following recurrence of a rectovesical fistula after a decade-long quiescent interval.

cially those with perianal disease in whom reconstruction of intestinal continuity is inadvisable. Although one-half of the patients with ulcerative colitis had TPC, only five (17%) of the Crohn's patients had primary TPC with a Brooke ileostomy.

Subtotal Colectomy (STC)

In CD complicated by carcinoma, STC was carried out in five (17%), a percentage somewhat less than the 25% in our UC patients. In only one was primary reanastomosis carried out. This is the preferred surgical procedure for UC patients who are ill, have severe active disease in addition to the cancer, are on steroids, are hypoalbuminemic and/or are severely anemic.

Palliative Procedures (PP)

Fewer than 5% of patients with CD or UC had cancers so advanced that they were inoperable. Palliative diversionary ostomy without resection was also necessary in an additional five (17%) of the patients with CD. The large number of unresectable cancers in CD was contributed to by the five patients with cancers in excluded loops. In earlier years, this operation was carried out frequently at The Mount Sinai Hospital, but is no longer done today. In most other series, cancers in excluded loops are less common.

Small Bowel Cancer in Crohn's Enteritis

Segmental resection was the preferred surgical therapy for Crohn's enteritis in 79% of patients (Table 2). Unlike the patients with colorectal cancer, only one patient developed cancer in nondiseased bowel. The four patients requiring palliative diversion, or who were inoperable, constituted 21% of the total series, a similar proportion to the 6 of 30 patients (20%) with CDCRC. Of these cancers, five occurred in excluded loops (15, 16, 18, 19).

Reticuloendothelial Tumors

Lymphomas

Lymphomas, colonic or extraintestinal (52), do not occur commonly in either CD and UC. It has been suggested that the incidence is greater than what was expected (4). For intestinal lym-

TABLE 2
Surgical Procedures for Cancer in Small Bowel in Crohn's Disease

	Subtotal n	Procedure n	%
Resection	15		79
small bowel resection		2	11
with ileostomy		1	5
with strictureplasty	1	5	
ileocolic resection and reanastomosis	11	58	
Palliative Procedures	4		21
bypass/diversion			
ileotransverse colostomy	1	5	
jejunostomy		2	11
inoperable		1	5
TOTAL	19		100

phomas, local excision is required. This should be followed by radiotherapy when indicated, and chemotherapy, which is the definitive therapy for extraintestinal lymphoma (52).

Leukemias

Leukemias are more common in ulcerative colitis than in Crohn's disease (4, 50) and occasionally may exacerbate the hemorrhage due to gastrointestinal ulceration. In one such patient with leukemia in CD, total proctocolectomy was required for massive gastrointestinal hemorrhage. Appropriate chemotherapy is necessary in all of these patients (50).

Cancers of the Anorectum

Low rectal adenocarcinomas in both forms of IBD and squamous cell cancers of the anus in Crohn's disease, usually with perianal disease, are treated by radical abdominoperineal resection of the rectum including the sphincter muscles, when necessary and resectable (53, 81). Early or advanced squamous cell cancers may be treated by local excision, or by radical excision with or without radical lymphadenectomy prior to radiotherapy and chemotherapy.

Peri-ileostomy Cancers

Cancers occurring at the site of an ileostomy are rare, but a number have been reported. Radical excision with transposition of the ileostomy is required (82).

Stricture Cancers

Cancers occurring in association with strictures constitute a particularly difficult diagnostic problem both for CDCRC (69) and UCCRC (70), in which the incidence of malignancy in strictures is approximately 30% and 5% respectively. When the diagnosis of cancer cannot be ruled out, surgical resection is indicated.

Small bowel cancer should be ruled out in all patients with multiple strictures in jejunoileitis in whom stricturoplasty is performed (15).

Cancer Occurring with Fistulae

This association has long been recognized (18, 19, 56, 59). Unfortunately such cancers are often unresectable. However, it is possible on occasion to carry out radical cancer "en bloc" resections, including the bowel on either side. This principle should be applied whenever the possibility of fistula cancer exists, even if unproven. If a complete cure is not possible, a longer period of palliation may be possible.

Long-Term Outcome Following Surgery for Gastrointestinal Cancer in IBD

Survival following surgical resection is better in colorectal cancer than in small bowel cancer in Crohn's disease. Although early series suggested a poor long-term outcome for UCCRC, recent studies have shown that survival is similar to that for non-colitic colorectal cancer. We have found a 45% 5-year survival for CRC in CD, which increases to 56% if cancers in excluded loops are omitted (unpublished data). This is comparable to the 52% survival for our 100 UC patients (80). For small bowel cancer, survival is much poorer, at best 23% at 3 years (15). Mortality for cancers in excluded bowel was 100% for both small and large bowel (see Fig. 5) (15, unpublished data).

Conclusions

Cancer in inflammatory bowel disease clearly increases in incidence in the intestinal tract and probably in certain extraintestinal sites as well. The absolute number of patients developing such malignancies are low compared to overall cancer rates in the general population, but because of higher relative risks, younger ages of onset, distinctive clinicopathological features, and difficulties in making a diagnosis, it is important that this complication of inflammatory bowel disease be widely appreciated. The prognosis today is no worse for colorectal cancers in ulcerative colitis or Crohn's disease (except for those occurring in excluded bowel) than for *de novo* cancers of the large bowel, but it remains exceedingly poor for small bowel cancers in Crohn's disease. Surveillance can probably be advised for ulcerative colitis-related colorectal cancers, although there is still some doubt as to whether it will be cost-effective or how it will affect prognosis and survival. There is even greater doubt concerning its role in monitoring patients with Crohn's disease for either colorectal or small bowel cancers. A cooperative study of endoscopic surveillance to diagnose dysplasia or malignant change in the mucosa of patients with Crohn's disease is now essential. There is increasing evidence that it would be rational to carry out surveillance for patients clearly at increased risk, namely patients with: unresected colons; longstanding disease (>10 years); and extensive disease, particularly in those with early onset of their Crohn's disease. The surgery for cancer in inflammatory bowel disease is based on a combination of the general principles for the surgery of IBD without cancer and radical excisional cancer surgery. Resection of the mesentery and lymphadenectomy should be carried out according to general cancer principles. Postoperative survival for colorectal cancer is good, approximately 50%, compared with the poor, less than 23%, survival for small bowel cancer.

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The Small Intestine

Charles D. Gerson, M.D.

Abstract

Clinical investigation of the small bowel at The Mount Sinai Hospital began with David Adlersberg's arrival in 1931. His research interests were in bile acids, cholesterol, carotene, and vitamin A. In 1952, he was given a Nutrition Laboratory and later, a Nutrition Clinic. His vitamin A tolerance test and interest in malabsorption led him to a comprehensive study of sprue, the separation of the tropical and non-tropical forms, and their different etiologies and treatments. Adlersberg's work was complemented by (a) Marshak and Wolf's radiologic examination of the small bowel (especially in sprue and other malabsorption disorders); (b) Gerson's perfusion experiments; and (c) Friedman, Waye and Wolf's motility studies. Lieber and his colleagues explored the deleterious effects of alcohol on the function and structure of the small intestine. Gerson explored the nutrition of patients with Crohn's disease of the small intestine, especially after extensive resection or bypass leading to ascorbic and folic acid deficiencies and hypergastrinemia. **Key Words:** Malabsorption, small intestine, jejunum, ileum, sprue, Crohn's disease, vitamin A, vitamin C, folic acid, alcohol.

The Small Intestine

The era of small bowel clinical investigation at Mount Sinai Hospital began with Dr. David Adlersberg in the 1940s. Having earlier established a reputation in the study of bile acids and cholesterol, in Vienna, he had the good fortune to be invited to The Mount Sinai Hospital in 1931 as a member of the Chemistry Department. He then extended his research interests to carotene and vitamin A. This led him to develop the use of the vitamin A tolerance test and a continuing interest in malabsorption syndromes. In 1952, The Mount Sinai Hospital established the Nutrition Laboratory under his supervision.

Celiac Sprue

In addition to the Nutrition Laboratory, Adlersberg had established a Nutrition Clinic where he followed a large number of patients with sprue. While non-tropical and tropical sprue had been recognized as clinical entities in the 19th century, their differentiation and the etiology of celiac sprue were not established until the classic report by Dicke, of the role of gluten, in 1952. However, in 1947, Adlersberg and Schein (1) published an extensive clinical description of a series of forty patients with sprue. This included findings of macrocytic anemia, steatorrhea, flat vitamin A tolerance test, and response to the diet then employed for sprue patients. Twenty-seven patients showed excellent response to a high protein, low fat, monosaccharide diet supplemented by liver extract, B complex and folic acid.

The first definitive description of villous changes in celiac sprue is attributed to Paulley in 1954 from surgical biopsy material. Schein (2), from Mount Sinai's Pathology Department, wrote an accompanying article to the above clinical description, also in 1947, from an autopsy of a patient with sprue. He described clubbing and mushrooming of small intestinal villi, "hitherto undescribed lesions of the intestine." This was clearly one of the first descriptions of an altered villous architecture in non-tropical sprue.

In 1951, Adlersberg and colleagues (3) were one of the first three groups to report on the beneficial effect of cortisone and ACTH in the treatment of sprue. The necessity for gluten restriction in the diet was not yet known so the treated patients were described as having refractory non-tropical sprue. Five of seven patients responded dramatically to steroids. In the early 1950s, this

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was a breakthrough form of therapy, as it still may be in patients resistant to a gluten-free diet.

In 1957, the *Journal of The Mount Sinai Hospital* published an entire issue devoted to sprue. Included was an article that summarized Adlersberg's experience with 94 patients with sprue (4). He was then able to define clinical and laboratory criteria that helped separate non-tropical and tropical sprue. This was the culmination of a long and productive career in the investigation of sprue.

Years later, in 1996, Kahn, Fiel, and Janowitz (5) returned to the subject of sprue with a report of a patient with celiac sprue and several autoimmune entities, including idiopathic thrombocytopenic purpura. In their article, they discussed HLA phenotypes and their possible role in the linkage of immunological conditions.

Tropical Sprue

Tropical sprue, another cause of malabsorption that is distinct from celiac sprue, was the subject of several research reports by Gerson. First, in collaboration with Lindenbaum (6), the small intestines of 68 Indian and Pakistani subjects who had come to New York were studied. Initially, these subjects were found to have functional and structural abnormalities known as subclinical tropical enteropathy. By following them sequentially, it was shown that their small bowels improved spontaneously after arrival in the United States. This indicated that environmental factors in South Asia were responsible for tropical enteropathy. Using a jejunal triple lumen perfusion technique, Gerson, Cohen, and Brown (7) were able to demonstrate the relationship between folic acid and hexose malabsorption in sprue. In the report by Meyers, Schweitzer, and Gerson (8), the occasional confusion and overlapping of findings between tropical sprue and pernicious anemia were clarified in a series of illustrative cases.

Radiology

Richard Marshak, best known for his radiologic studies of inflammatory bowel disease, was interested in all aspects of small bowel radiology. One of his interests was sprue. In collaboration with Wolf and Adlersberg (9), he published the first large series of sprue patients in 1954. With his typically critical eye, he described the radiologic characteristics of sprue that distinguished it from other small bowel diseases. He was one of the first to emphasize proximal dilatation as the earliest change. He also complemented Adlersberg's work by demonstrating x-ray improvement after steroid therapy.

Marshak published numerous articles on various small intestinal disorders, and became a national and international expert in this area. His weekly radiology conference at The Mount Sinai Hospital was avidly attended by physicians from near and far. His observations were finally recorded in a classic medical text, "Radiology of the Small Intestine" (10), published in 1970.

Motility

The next investigative work concerned small bowel motility. In the 1950s and 1960s, knowledge in this area was limited, in part due to the technical difficulties in studying the small intestine. Motility research was largely confined to the proximal small bowel. Gerald Friedman and Jerome Waye (11) developed a new technique utilizing pressure transducers and a series of three catheters with openings 7 cm apart. These were placed in the gastric antrum, and various levels of the duodenum and proximal jejunum. They began to describe, in several reports, the differentiation of various wave types in the duodenum. In collaboration with B.S. Wolf (12), they correlated pressures with cineradiographs so that pressures could be compared with motility patterns. They appreciated that there were propulsive contractions and mixing contractions. At that time, techniques for measuring the migrating motor complex, especially phase III with its "housekeeping" function, had not yet been developed.

Alcohol

Charles Lieber is best known for his work on alcohol and the liver (13). However, his experimental model of feeding alcohol while maintaining normal nutrition was also utilized to study the effects of alcohol on the small intestine. In 1969, in collaboration with John Lindenbaum (14), he published the first report to show that alcohol inhibited intestinal absorption of vitamin B_{12} despite the presence of intrinsic factor and pancreatic enzyme. This finding led to a more extended study of small intestinal structure and function. Several articles documented anatomical changes. Emanuel Rubin and colleagues (15) showed electron microscopic changes in mitochondria, endoplasmic reticulum and cytoplasmic degradation, both in jejunum and ileum. Later (16), histologic changes were demonstrated with an increase in crypt-villous ratio, cellular infiltration of the lamina propria, and some erosion of villous tips.

Perlow and Lieber (17) also measured enzyme activity in the brush border of chronic alcoholic men. There appeared to be diminution in sucrase activity and lactase activity, compared with controls. These enzyme levels increased after two weeks of abstinence; there was an increase in both enzymes, suggesting that alcohol was responsible for the findings.

Crohn's Disease

In the 1970s, Gerson published a series of papers related to the effects of Crohn's disease on small intestinal absorption and nutrition. In an effort to correlate ileal disease or resection with absorptive parameters, 68 patients with ileitis were studied (18). Resection of 90 cm of terminal ileum was a major determinant of steatorrhea, while resection of 60 cm uniformly caused vitamin B-12 malabsorption. Jejunal function was well maintained in most patients except those with short bowel syndrome whose absorption parameters were most impaired. This study emphasized the nutritional consequences of intestinal resection, which then was performed more freely than it is today.

One of the consequences of extensive intestinal resection with a resultant short bowel syndrome is gastric acid hypersecretion. In the early 1970s, Straus and Yalow were able to measure serum gastrin levels in a series of patients with short bowel syndrome in whom hypersecretion of gastrin was the probable cause of excess acid (19). It was suggested at that time that some inhibitory factor had been removed in the resected distal small bowel, but this hypothesis has still not been clearly established.

Patients with Crohn's disease often avoid fruits and vegetables because of problems with diarrhea. Because it was known that this dietary restriction may cause folic acid deficiency, Gerson and Fabry studied another vitamin present in the same foods, ascorbic acid (20). Serum and leukocyte ascorbic acid levels were significantly reduced, sometimes in the range seen in scurvy. Dietary histories showed that vitamin C deficiency was correlated with reduced ascorbic acid intake.

Because ascorbic acid is important for collagen formation, tissue ascorbic acid concentration was then measured in surgical ileal specimens from patients with and without fistulae. Both tissue and serum ascorbate levels were significantly lower in patients with fistulae. This study demonstrated that vitamin C deficiency can be a nutritional consequence of Crohn's disease.

Folic Acid Absorption

Another area of active investigation by Gerson and co-workers (21) included the use of a triple lumen tube to perfuse various substances over a 30-cm segment of proximal jejunum. Fluid aspirated from the distal port of the perfusing system could be used to measure accurately the absorption of various solutes, such as folic acid. Adding other substances to the perfusate could be shown to affect folate absorption. Glucose increased the absorption of folic acid, possibly due to solvent drag. Diphenylhydantoin (DPH), on the other hand, when added to the perfusate (22) was shown to inhibit folate absorption, thus explaining the association between DPH and folate deficiency. Folic acid absorption was found to be normal in patients with Crohn's disease (23). Acetazolamide inhibited the absorption of salt and water by the normal human jejunum (24).

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Editor's Note

SHERMAN KUPFER, M.D.

WITH THIS ISSUE, *The Journal* presents the second in its series, edited by Drs. J.H. Baron and Henry D. Janowitz, intended to introduce significant contributions made by Mount Sinai staff to gastroenterology and hepatology over the course of almost a century and a half. Dr. Baron, in particular, has done herculean work in digging out information from the archives and locating early publications, to present as complete and accurate an account as possible.

While preparing the material for publication, it became readily apparent that two articles originally published in 1932 merited special consideration, not only for their historical context, but also for their medical content. These articles are therefore republished here, to afford easy access both in print and electronically, via the Web. One of these articles, by Ginzburg and Oppenheimer, originally appeared in *Transactions of the American Gastroenterological Association*; the other, by Crohn, Ginzburg and Oppenheimer, appeared in the *Journal of the American Medical Association*. These two articles were originally delivered as oral presentations in early May 1932, the presentation by Ginzburg preceding that by Crohn.

The article by Ginzburg and Oppenheimer has rarely been cited in the medical literature, probably because the journal was neither widely distributed nor easily available. In fact, there is some question as to whether the two listed authors ever knew of its publication, since they never cited it. A later version of this same article, embellished with relevant figures of pathological specimens and clinical radiographs, appeared in 1933 (Annals of Surgery 98:1046-1062).

This, of course, was not the case for the 1932 article by Crohn, Ginzburg and Oppenheimer which appeared in *JAMA*. Both articles provided valuable, if not similar, insights into a disease which often had been described earlier, as Baron points out. But now, Crohn's oral presentation catapulted this disease entity into the consciousness of the medical community. And from this moment, progress in treating the disease would be relentless, thanks to a more thorough description of its clinical course and an improved grasp of its pathophysiology, and the cellular and molecular events with which it is associated.

The Journal will continue to republish accounts of important contributions made by Mount Sinai staff, from its own archives as well as from other publications, particularly where hard copy access may be limited or difficult. I hope that our readers will find this useful.

Landmark Article

Transactions of the American Gastro-enterological Association 1932; 35:241 – 283.

Non-specific Granulomata of the Intestine*

(Inflammatory Tumors and Strictures of Bowel)

Leon Ginzburg, M.D., and Gordon D. Oppenheimer, M.D.

During the past few years, we have encountered cases, apparently with increasing frequency, which clinically and radiologically gave the impression of being tumors or tuberculosis of the bowel. At operation, these cases were usually considered to be either hypertrophic tuberculosis or malignant disease. Microscopic examination of resected specimens, however, failed to substantiate these views. No evidence of specific disease, such as tuberculosis, syphilis, or actinomycosis, could be found. Amoebic disease of the bowel was excluded both from a study of the sections and the stool, as well as by the inefficacy of emetin therapy in suspected cases. Carcinoma, lymphosarcoma, and Hodgkin's disease could be definitely excluded. A few of these cases were quite evidently secondary to diverticulitis, but aside from these, a large heterogenous group remained, differing etiologically, but with certain common clinical and pathological findings. These cases, which showed various degrees of hypertrophic chronic inflammatory lesions in different stages of healing have long been known to the English as well as the Continental surgeons. In 1921 Tietze (1) published a thorough resume of the subject with a very complete bibliography. In 1923, Wilensky and Eli Moschkowitz (2) reported four cases which they had collected from various institutions, using the designation "Non-specific Granulomata of the Intestine," a name, which perhaps best conveys an idea of the underlying pathology. Mock (3) has recently reported a series of cases using the same designation. Clinically these cases manifest themselves either by the development of palpable masses or symptoms due to an ulcerative stricturing of the bowel. They may, therefore, with propriety, also be designated as non-specific inflammatory tumors and strictures of the bowel.

It is well known that both the intestine and its peritoneal covering have tremendous powers of resistance to infection and a marked ability to resolve inflammatory lesions. Furthermore, the intestinal mucosa is possessed of marked regenerative power (4). Surgeons have time and time again recorded their amazement at the rapidity and completeness of the disappearance of huge inflammatory exudates and masses from the abdomen. Similarly, both clinically and experimentally we know that there may be extensive mucosal disease or injury without any resultant permanent scarring. In some instances, however, following an infection or injury, this "restitutio-ad-integram" does not occur. The persistence of some infectious agent or irritating factor, or the inability of the tissues to overcome them, results in a cycle of reparative and destructive processes which leads to the formation of either hypertrophic extra-intestinal masses or extensive intramural hypertrophic ulcerative stenotic lesions or combinations of both.

Histological study of the various types of lesions shows simply evidences of various stages and degrees of acute and chronic inflammation with lymphocytic, polymorphonuclear and plasma cell infiltration, with varying degrees of degenerative changes or fibroblastic proliferation. In some of the periintestinal lesions there is considerable hyalinization, and early calcification and even early bone formation have been encountered. The presence of giant cells is a common finding. We believe that these are accidental findings due to the presence of non-absorbable vegetable matter, minute quantities of which extravasated around the lesion in perforative cases or became entrapped in the healing of ulcerative lesions. Wilensky and Moschkowitz reported the presence of large cells in the section of one of their cases. By special stain, we have been able in a number of our cases to demonstrate cells or groups of cells with much cytoplasm and little nuclear material, which are in all probability, vegetable cells. These apparently became entrapped in healing ulcers and were apparently taken up by the lymphatics, for we have found them in the serous and subserous layers of the bowel, as well as the submucous. Being nonabsorbable, they become encapsulated by foreign body giant cells. In the serosa they give rise to little nodules which are very difficult to differentiate grossly from miliary tubercles. Such foreign body tubercles, incidentally, have been experi-

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mentally produced by the introduction of emulsions containing vegetable matter into the peritoneal cavity (5). We consider them as accidental, rather than etiological factors, in the course of the disease. Their importance is two-fold; firstly, their irritant action may be a factor in producing the marked hyperplastic fibrosis seen in some cases; and secondly, they are probably responsible for the confusion of these non-specific lesions with tuberculosis.

The following is a study of fifty-two cases which have been observed and operated upon mainly on the surgical service of Dr. A. A. Berg during the last ten years. Only those cases where resection was performed or specimens obtained are considered. These sections were restudied with the invaluable aid of Dr. Paul Klemperer to help us in settling questionable points. These do not include cases of sigmoid diverticulitis or any lesions situated distal to the recto-sigmoid junction. Gastric cases and two cases of ulcerative jejunitis near the fossa of Treitze have also been excluded from this study. An accurate etiological or pathological classification is at present impossible. We submit the following classification therefore, fully conscious of its defects and overlappings, but pleading in its favor, a certain degree of clinical utility. It is our plan to discuss each group and to report in abstract some of the typical cases.

1. Extra- or peri-intestinal granulomata secondary to sealed-off perforations of the bowel.
2. Granulomata secondary to known vascular disturbances of the gut.
3. Localized hypertrophic ulcerative stenosis of the terminal ileum.
4. Localized hypertrophic colitis with or without low-grade generalized colitis.
5. Simple penetrating ulcers of the colon.
6. Lesions secondary to inflammation of the appendages of the bowel, such as appendicitis, diverticulitis, typhlitis.

I

Lesions in Which the Inflammation Reaction Is Mainly Extra- or Peri-intestinal and Which Are Secondary to Sealed-off Perforations of the Bowel

As a response to a slowly perforating lesion of the intestine that has become sealed off by omental, parietal, or visceral adhesions, large inflammatory masses, with very little or no pus formation may develop, which are intimately adherent to the serosa and sub-serosal tissues but do not actually involve the sub-mucosal and muscular layers of the gut. A classical example is the type of lesion resulting from perforation of the colon by such foreign bodies as fish bones. Usually this accident results in the formation of ordinary intra-abdominal abscesses. In some instances, however, probably due to the slow rate of perforation, the inflammatory reaction is mainly productive. As a result of the continued presence of the foreign body and the low-grade infection resulting from the penetration of the intestinal wall, a markedly hypertrophic inflammatory reaction takes place in the peri-colonic and sub-serous layers of tissue which both clinically and at the operating table may give the impression of being a colonic neoplasm. Three such cases operated upon under the clinical diagnosis of neoplasm were recognized for their true nature at the time of operation and the foreign bodies sought for and found. Perforative lesions, from whatever cause, may involve the omentum with the development of a large omental mass containing necrotic xanthematous tissue, firmer fibrotic masses, areas of calcification or discrete encapsulated miliary abscesses. The lesion in the wall of the gut may be minimal.

An exceedingly interesting group are those cases in which a pseudo-tumor of the abdominal wall itself develops as a result of a perforative lesion, becoming sealed off by the anterior parietes. In two such cases, foreign bodies (fish bone, toothpick) were found in the center of large firm tumor masses involving the rectus muscle and pro-peritoneal tissue. These tumors had been excised under the diagnosis of sarcoma of the abdominal wall. The deep side of these inflammatory abdominal wall tumors was densely adherent to the omentum but there was no evidence of adherent bowel. In two other cases, in which the same preoperative diagnosis of sarcoma was made, adherent gut was found on the deep side of the tumor mass; a perforation apparently having been sealed off by the parietal peritoneum. The "tumors" were found to be edematous, granulomatous lesions involving the parietal peritoneum and the pro-peritoneal cellular tissue.

Altogether, ten cases were encountered in this group, five of which were definitely due to foreign body. In three cases, the inflammatory mass was mainly in the serosal and subserosal layers of the flexures of the colon. In two instances, the mass was mainly omental; the original perforation being in the transverse colon in one instance and in the small gut in the other. In four cases, the main mass and granulomatous tissue lay in the abdominal parieties, and in one instance was chiefly peri-vesical. (The large group of cases with marked productive peri-cecal changes due to appendicitis and peri-sigmoidal inflammatory masses from sigmoid diverticulitis also belong in this group, and are much more common than any of the other types of lesions noted. They are so well known, however, that they have not been especially studied or included in the enumeration of this group.)

Clinically these cases are characterized by the development of a palpable mass without the appearance of symptoms due to obstruction or ulceration. Because of the lack of intramural involvement of the bowel the barium meal or enema usually shows no abnormalities. Occasionally, a persistent spasm of the bowel adjacent to the lesion may be encountered which gives the impression of a filling defect. At operation, these tumors are found not to encroach upon the intestinal lumen and intra-intestinal irregularities or ulcerations are absent. This point serves to differentiate even the very adherent and intimately connected peri-intestinal masses from neoplasm or inflammatory diseases which actually involve the bowel walls.

1. Case of large peri-intestinal inflammatory tumor originating in the small bowel

E. H., age forty-five, admitted to Mount Sinai Hospital in 1925. Two years ago a laparotomy had been performed in the lower abdomen. Did not know what operation had been performed. She was well until few months before admission when she began to experience localized abdominal tenderness, some constipation and loss of weight. Physical examination revealed a large mass, the size of a grapefruit, to the left of the midline adherent to the scar of the old operation. No evidence of any hernia at this point. G. I. x-ray was negative. Colon enema negative.

At operation, tumor was resected with the adherent skin and fascia and muscle. On its deep surface it was intimately adherent to and apparently an integral portion of the wall of the small intestine. This portion of the bowel together with the tumor was resected.

Pathological report. — "Macroscopic specimen consists of a tumor mass, the size of a large grapefruit, adherent to the skin and by its deep surface to a small segment of small intestine. The skin and intestine appeared to be normal. The tumor itself, is of a mottled character, darker portions appearing like hemorrhagic inflammatory tissue. The lighter yellowish portions are evidently the seat of necrosis. Below the attachment to the skin is a small, hard piece of tissue which cannot be cut, and which may be either foreign body or possibly new bone formation. The portion of tumor not adherent to the gut is covered by a thin sheet of tissue probably compressed omentum. Grossly, it cannot definitely be determined whether tissue is inflammatory or neoplastic in nature. Microscopic examination: shows no evidence of neoplasm. There is considerable acute and chronic inflammation with areas of fibrous tissue, areas of necrosis, hyalinization, calcification and ossification."

The patient made an uneventful recovery. Six months postoperatively she was well. Has not been seen since.

2. Case of peri-colonic inflammatory tumor, mainly omental, simulating sarcoma of the bowel. Healed colonic perforation

D. S., age fifty-three, admitted to the Mount Sinai Hospital in 1922. Nine months before admission he had developed pain in the right lumbar region. After three months, the pain became most marked in the right lower quadrant where it had persisted to the time of admission. The pain was dull and boring, and radiated posteriorly. It was more or less continuous and bore no relation to either meals or bowel movements. There had been no change in the character of the alimentary habits. Physical examination revealed a palpable mass in the right lower quadrant opposite the umbilicus, the dorsal portion of which appears to be fixed. Wassermann was negative. X-ray showed spasticity of the transverse colon and an apparently persistent defect in the caput coli. Whether this defect was due to new growth or to spasm could not definitely be determined from the roentgenogram.

At operation a mass was found adherent to the parietal peritoneum. The peritoneum was opened below this point and separated. There did not appear to be any involvement of the inside of the bowel wall. The mass was thought to be sarcomatous and accordingly, resection of the transverse colon with the adherent tumor and omentum was performed.

Pathological examination. — Macroscopic specimen consists of resected transverse colon with a portion of mesentery and adherent omentum. At about the central portion of the specimen is a small mucosal scar extending through the wall and at this site thickened omentum is densely adherent. No definite perforation can be established. The omentum proper is markedly infiltrated and is the seat of numerous abscesses, varying from 1 to 3 cm. in diameter. Diagnosis: Inflammatory tumor of the omentum with multiple encapsulated abscesses.

3. Case of fish-bone perforation with peri-colonic mass

A. K. was admitted to the Mount Sinai Hospital in July, 1926, with a complaint of pain in the left upper quadrant of the abdomen of eight weeks' duration. The pain was localized, and did not radiate. It was more or less constant and had no definite relation to the intake of food. For the last three weeks, the bowels had moved only with the aid of cathartics. The patient also stated that the stools had become smaller in diameter. There was no melena, vomiting or diarrhea, nor were there any urinary symptoms. He had lost twenty pounds in weight since the onset of his illness. However, he appeared to be fairly well nourished and his hemoglobin was 95 per cent. In the left upper quadrant of the abdomen, and in the left flank, a slightly tender, large mass was palpable. X-ray and pyelogram of the urinary tract showed the kidney to be normal in size and in position. X-ray of the colon showed no filling defect. A pre-operative diagnosis of inflammatory tumor or carcinoma of the splenic flexure was made.

At operation, a large mass was found occupying the splenic flexure and upper portion of the descending colon. This was carefully separated into two component parts, one of which consisted of thickened, inflamed omentum; the other was a large smooth, firm peri-colonic mass. There was no evidence of any invasion of the colonic lumen. In the midst of this mass there was seen to be a depressed area, of what was apparently a healed fistulous communication with the gut. The omentum mass was then further explored and two fish bones were found lying in separate small abscess cavities. The abdomen was closed with rubber tube drainage and the patient made an uneventful recovery.

4. Case of fish-bone perforation with formation of inflammatory tumor of the abdominal wall

J. C., age sixty-five, was admitted to the Mount Sinai Hospital, April 30, 1925. For the past few months the patient had noted the development of a mass above and to the right of the umbilicus. There had been no pain associated with its development. It had never been reducible. Physical examination showed a hard, smooth, spherical mass about three inches in diameter, to the right and above the umbilicus. It was not tender and there were no signs of inflammation. There was no cough impulse. The preoperative diagnosis was that of a tumor of the abdominal wall.

An elliptical incision was made around the mass and the tissues found to be normal down to the rectus muscle. The posterior aspect of the rectus muscle, the posterior rectus sheath and peritoneum were involved in a mass of dense, grayish tissue. To effect its removal, the abdominal cavity had to be entered. The omentum was then found to be adherent to the mass, but was not apparently involved in the inflammatory process. There were no evidences of any adhesions of any of the abdominal viscera to the deep surface of the tumor. The tumor, when excised, was still considered to be a neoplasm, and the specimen was cut across for further inspection. In the depths of the mass a small collection of pus was found, and in its center was a fish bone, 2 to 3 cm. long. Culture showed staphylococcus albus and an anhemolytic streptococcus.

The pathological description follows: "The macroscopic specimen consists of tumor mass to which is attached a resected portion of omentum and some adherent muscle. The tumor mass measures about 7 to 8 cm. in diameter, is oval in shape, firm in consistency and on section presents a small sinus tract, containing a foreign body about 3 cm. long (fish bone). Microscopic examination discloses a fibroma showing numerous inflammatory areas. A few multinuclear giant cells are present, in the tissue adjacent to the foreign body."

II

Lesions Secondary to Known Vascular Disturbances of the Bowel

The most striking example of this type of lesion that we have encountered is the stenotic involvement of the bowel, resulting when badly compromised but viable gut has been replaced following operation for strangulated hernia. In these cases there is permanent vascular injury affecting the intramural vessels of the bowel. Vascularization through anastomosis is sufficient to prevent a necrosis of the muscular and fibrous layers of the bowel. It is, however, insufficient to permit of the usual marked regenerative functioning of the intestinal mucosa. Ulcerative lesions involving the mucous membrane first result, followed by secondary infection and the production of gradual fibro-stenotic reactions which may result in extreme reduction of the caliber of the intestinal lumen. Five such cases have been encountered in this series, all in the form of a tubular stenosis, i.e., cases in which the entire segment of strangulated gut underwent fibrotic involution. In the literature, cases of narrow annular stricture corresponding to the site of constriction at the neck of the sac have been reported. In this series we observed one annular stricture in which a loop of gut had been caught under an encircling band of omentum. Small mesenteric tears have been reported as causing stenosis, both clinically and experimentally, in the same manner.

The symptoms are those of gradually increasing subacute intestinal obstruction, the ulcerative phase apparently passing by unnoted. The symptoms have appeared anywhere from two weeks to six months following strangulation. Short circuiting entero-anastomosis effected relief of symptoms in four cases; resection in one. One patient came to autopsy without operation.

In these cases we have definite evidence from the history and findings at the primary operation that there had been extensive vascular insult. How large a role this vascular mechanism plays in cases where the causal connection is not so clear-cut, it is difficult to say. The fact that such lesions as repeated and self-reducing intussusceptions or recurrent partial volvulus, especially at the ileo-cecal angle, may be responsible for certain chronic inflammatory lesions, must be borne in mind, although insusceptible of proof. It must be emphasized that the end stages of a lesion in which primary vascular insufficiency permitted necrosis and secondary infection of the bowel resemble almost identically those in which a primary infectious agent has produced secondary thrombotic and degenerative changes.

I. M. L., age forty-five, was admitted to the Mount Sinai Hospital in September, 1926. She had been operated on four years ago at another hospital for a left inguinal hernia, which had apparently recurred shortly afterwards. Eight hours before admission it had suddenly become large, painful and irreducible. She had vomited three times. Examination revealed an irreducible inguinal hernia about the size of a small grapefruit.

An immediate operation was performed, and a bilocular sac containing brownish, slightly foul-smelling fluid, was found. Two loops of intestine were found to be incarcerated, one of which showed considerable cyanosis with subserous hemorrhage. After a prolonged period of observation and irrigation with warm saline, the loop was considered viable and was replaced. The subsequent course was uneventful, and the patient was discharged well at the end of two weeks.

For four months following the operation the patient was apparently entirely free from symptoms. At that time she began to experience occasional attacks of colicky abdominal pain. There was no vomiting or constipation. Shortly afterwards, the patient was seen in the return clinic and visible peristalsis noted. A gastrointestinal x-ray was taken which showed unmistakable evidence of an incomplete small intestinal obstruction. Laparotomy was advised but refused. One month later, the patient was readmitted to the hospital in a moribund condition with signs of intestinal obstruction. Her condition was too poor to warrant operation. Respirations ceased soon after admission.

Autopsy showed the following: "Eighty cm. above the ileo-cecal junction, the intestine shows a narrowing 8 cm. long. The area is about one-third the diameter of the normal intestine. The ileum proximal is markedly dilated. In the region of the stricture the wall of the intestine is markedly thickened and the lumen markedly stenotic. The mucosa is cicatricial and there are polypoid excrescences of the preserved mucosa. Microscopically the wall of the ileum is seen to be several times normal in thickness. The mucosa is denuded of epithelium; the muscularis mucosa is fragmented. There is a marked inflammatory infiltration of submucosa and subserosa."

III

Hypertrophic Ulcerative Stenosis of the Terminal Ileum

In this group of cases the terminal ileum is the seat of the lesion, the changes being most marked at the ileo-cecal valve where it usually terminates abruptly on the ileal side of Bauhin's valve. Proximately, it diminishes in severity, signs of the disease being rarely found further than 10 to 15 inches from the cecum. We have no clue to its etiology but observation of various stages of the disease in different patients lead us to believe that the following are the steps in the development of the final process. The primary lesion, we believe, are a number of oval or lenticular shaped ulcerations located on the mesenteric side of the bowel. We have found this lesion on a number of occasions proximal to the main, hypertrophic mass and separated from it by normal looking mucosa. As the disease progresses, it is characterized. by two main features; firstly, a marked tendency to perforation and secondly, by an excessive proliferative reaction in the submucosa. The end stage of the process, the one most frequently encountered, is manifested by the conversion of the terminal ileum into a thickened hose-like tube. When opened, the normal transverse intestinal folds in the terminal portion of the bowel are seen to be partially destroyed and partially flattened and broken up into polypoid masses. A series of linear ulcerations along the mesenteric border is practically a constant finding. At times, especially near the cecum, the mucosa is almost completely atrophic and there may be papillary excrescences, especially along the margins of the ileo-cecal valve. The submucosa is enormously thickened and causes a marked diminution in the caliber of the lumen. Perforation frequently occurs in between the leaves of the mesentery and the enlarged glands and exudate gives rise to good-sized masses. The pus may track along the cellular tissue and form secondary communications with the cecum or colon. At times the perforation occurs into the peritoneal cavity with the formation of an intra-peritoneal abscess. Drainage of these abscesses results in the formation of intractable fistulae. Clinically, these patients have presented themselves with four different pictures.

1. Simulating acute appendicitis. — The first sign of the disease may be an attack impossible to differentiate clinically from appendicitis. At operation however it is at once noted that the terminal ileum is soggy, edematous and blotchy, and that there are numerous large succulent glands in the terminal mesentery. Resection has never been performed in this stage of the disease in this series, so that we have no idea of the underlying pathological changes present during this phase. A number of these patients gradually passed into the more chronic phases of the disease. One case is symptom-free two years after exploration, although x-ray shows definite narrowing in the terminal ileum.

Occasionally these patients are admitted with an abscess already present. Drainage may result in the formation of a chronic fistula starting immediately post-operatively, or there may be primary healing with secondary breaking down, occurring weeks or months later.

2. Symptoms of ulcerative enteritis. — There may be a low-grade diarrhea, loss of flesh and strength, mild colicky pains, and a development of a secondary anemia. This type is rather uncommon.

3. Symptoms of chronic incomplete small intestinal obstruction. — This is the most common manifestation of the disease. The patient may previously have passed through one of the phases described above, but frequently the obstructive symptoms appear without any previous history. Severe abdominal cramps, visible peristalsis, and borborygmus are the most common symptoms complained of. The duration of symptoms in this group varies from one to three years. At operation the typical hose-like ileum referred to above, frequently very densely adherent or communicating with the cecum, ascending colon or sigmoid is found. The occasional presence of small tubercle-like nodules may serve to render differentiation from tuberculosis more difficult. The nature of these foreign body tubercles has been discussed above.

A mass was palpable in every subacute and chronic case. Visible peristalsis was frequently noted. The barium enema as a rule shows no abnormality, as the disease ends at the ileocecal valve. As a result of pathological ileo-colic or ileo-sigmoidal communications, secondary changes may occur in the colon which are reflected in the barium enema and which may lead to a false conception as to the true nature of the pathological process. In two instances, definite narrowing has been demonstrated in the terminal ileum following the barium meal. In others, dilated loops of ileum and ileal stasis have been demonstrated. In most of these cases no attempt was made to administer a barium meal because of a fear of causing a complete obstruction.

4. Chronic intractable fistulae. — These have resulted following drainage of intra-abdominal abscesses, and have resisted closure by exposure and simple suture of the internal opening plus enterostomy. They have been cured either by short-circuiting operations with exclusion of the involved loop, or resection of the diseased segment plus entero-colostomy. The findings at operation are those described tinder the chronic form of the disease plus the presence of extensive adhesions.

There have been fourteen ileo-cecal resections in this group with one death. Of the remaining thirteen cases, one patient returned with an annular stricture a few inches proximal to the site of the original resection. The other cases have done well. We have only two proven cases where a previous short-circuiting operation with exclusion had been performed, both these cases later coming to resection. In one of these, an anastomosis had been performed elsewhere apparently through disease tissue with a resultant implantation of the disease on the colonic side of the anastomosis. Another patient, on whom an entero-colostomy with exclusion had been done, developed a new focus of the disease involving a segment of gut five or six feet proximal to the original area. There were four other patients who, we believe. fall into this group, in whom entero-colostomy exclusion proved curative. No specimens were, however, removed from these patients and they are not definitely included in this group.

Relation to Appendicitis

We do not believe that this group of cases has any relation to appendicitis. Approximately half of these patients had been subjected to previous appendectomies. In some of them, it had already been noted at the time of the primary operation, that distinct abnormalities were present in the terminal ileum. In those patients in whom the appendix was still present at the time of resection, no particular abnormalities were found in it, aside from a severe peri-appendicitis.

Relation to Tuberculosis

Careful study of these sections revealed no definite tubercles, no caseation, necrosis, nor could tubercle bacilli be demonstrated. In six instances, guinea pig inoculation, inoculation into rabbits and into chickens failed to show evidence of any variety of tuberculosis. Lowenstein cultures for tuberculosis were negative in three instances.

It might be argued that evidences of tuberculosis would be difficult to find in tissue which has undergone fibrosis. However, anatomical tubercles and the Koch bacillus could not be demonstrated even in the active ulcerative lesions found proximal to the main hypertrophic mass. Even in the tubercle-like structures occasionally seen on the serosa, definite evidence of Koch infection could not be found. During the past ten years there have been only five cases of localized hypertrophic tuberculosis resected at operation at the Mount Sinai Hospital. There have been a number of instances of multiple tuberculous foci in the intestines found at laparotomy. There have also been a number of cases with active or advanced pulmonary tuberculosis with x-ray evidence of involvement of the ileo-cecal region. In the latter instance, operation was never resorted to.

To sum up our impressions of localized hypertrophic tuberculosis, it has been our experience that most of the supposedly localized ileo-cecal tuberculosis proved on microscopic examination to be non-tuberculous, while on the other hand, most of the indubitably tuberculous lesions proved to be unsuitable for resection because of their multiplicity.

Case of hypertrophic stenosis of the terminal ileum, foreign body tubercles present

A. P., age thirty-six, was admitted to the Mount Sinai Hospital, July, 1930. Eight years ago an appendectomy had been performed, apparently for chronic appendicitis. The present illness was of two years' duration, first manifesting itself by weakness and loss of weight. Eighteen months before admission severe peri-umbilical pain had developed and had gradually increased in severity until it was almost continuous. She had suffered from moderate constipation until the last few weeks, when mild diarrhea movements, three to five per day, occurred. She was asthenic and had lost thirty pounds in two years. Physical examination revealed a mass, the size of an orange in the right lower quadrant, behind the old appendectomy scar. Hemoglobin was 50 per cent, Wassermann was negative. Stool showed no blood, ova or parasites. Barium enema showed dilatation of the entire colon with marked redundancy of the transverse colon. X-ray following barium meal showed some degree of ileal stasis. A preoperative diagnosis of either carcinoma or tuberculosis of the ileo-cecal region was made.

Operation revealed a large inflammatory mass involving the terminal ileum, cecum and ileo-cecal mesentery. There was a large mass of nodes along the right colic artery. Tubercle-like structures were found on the serosa of the terminal ileum. The post-operative diagnosis, following a resection of the terminal ileum, cecum and ascending colon was ileocecal tuberculosis.

Pathological description. — "Resected specimen consists of 12 cm. of ileum, cecum and ascending colon. Ileo-cecal junction is markedly thickened, forming a tumor the size of a tangerine. The mucosa of the ileum shows areas of ulceration as well as some areas of mucosal hyperplasia. Some of the ulcers appeared to be surrounded by tubercle-like structures. The ileo-cecal orifice was markedly narrowed and the wall of the valve infiltrated by dense connective tissue. The cecal wall also appeared hyperplastic but the main lesion seemed to stop at the valve. The serosa of the ileum and cecum presented a few discrete millet-sized tubercles."

Histological examination.—Marked thickening of all the layers of the gut due to fibrous proliferation with diffuse infiltration of large and small lymphocytes, monocytes, plasma cells and occasional polynuclear leucocytes. There are also areas of lymphoid hyperplasia. The mucosa shows ulceration. No tubercle bacilli seen. No anatomical tubercles seen. No evidence of caseation necrosis.

Numerous giant cells were seen and large cells and groups of cells with pale cytoplasm and small nuclei. These were considered vegetable cells with foreign body reaction.

Portions of the lesion were ground up and injected into rabbits, guinea pigs and chickens for tubercle bacilli identification. All were negative. Final pathological diagnosis: nonspecific chronic and acute productive and ulcerative inflammation of the lower ileum.

8. Hypertrophic stenotic inflammation of terminal ileum with obstructive symptoms, spontaneous perforation into sigmoid. Preoperative diagnosis: Carcinoma of sigmoid

Male, D. H., age twenty-six, admitted to the Mount Sinai Hospital in October, 1928. For three years he had been suffering from severe abdominal colic and constipation. At times diarrhea had been present. There was no bloody stool. He had lost considerable weight, the exact amount was unknown. No anemia. Physical examination revealed moderate abdominal distention. Rectal examination showed a mass rather toward the left side of the pelvis which could be palpated bimanually and was interpreted as being a sigmoid mass, prolapsed into the cul-de-sac. Barium enema showed a stricture of a mid-sigmoid which, at that point was narrowed to the size of a quill. Preoperative diagnosis was carcinoma of the sigmoid.

Operation. — Terminal portion of ileum was found densely adherent to cecum and both were bound down to mid-sigmoid. Upon freeing the adhesions it was seen that there was an ileo-sigmoidal fistula. Aside from this site of perforation, the sigmoid appeared normal. It was realized that the main lesion was in the terminal ileum. The opening in the sigmoid was therefore closed in layers and a typical ileo-colectomy performed for the removal of the mass involving the ileum and cecum.

Pathological examination. — Resected specimen consists of 33 cm. of ileum and the cecum. The proximal 17 cm. of the specimen consist of normal but markedly dilated small gut. The distal half of the resected gut is considerably narrowed and its walls thickened. The narrowing of the lumen and the thickening of the wall increase toward the cecum. The thickening is due mainly to hyperplastic changes involving the submucosa and the mucosa. A series of superficial irregular ulcerations with reddish green base are seen throughout the stenosed portion of the ileum always at the mesenteric insertion. About 6$^1/_2$ cm. from the cecum there is an irregular hemorrhagic area about 1$^1/_2$ cm. in diameter with a centrally placed irregular perforation. About 1 cm. from the ileo-cecal junction is a large superficially ulcerated area from which pus escaped on pressure. Aside from these ulcerated areas the mucosa is edematous and has a cobble-stone appearance. The lymph nodes are hyperplastic.

Histological examination.—Marked mucosal ulceration with acute and chronic purulent inflammation. Diffuse thickening of all layers of the gut especially the submucosa due to edema granulation tissue and diffuse infiltration with large and small lymphocytes, plasma cells and occasional polynuclear leucocytes and occasional giant cells. No tubercles or tubercle bacilli seen. Final pathological diagnosis: Hyperplastic chronic ulcerative inflammation of ileum. Picture resembles hyperplastic tuberculosis of the ileo-cecal region but there is no evidence of tuberculosis in this instance.

9. Operation for acute appendicitis. Diseased terminal ileum noted at the time. Gradual development of obstructive symptoms. No relief from ileo-colostomy. Resection performed.

S. W., age thirty, operated at another institution on March 1, 1929, with a preoperative diagnosis of acute appendicitis. At operation, it was noted that the ileo-cecal junction and the terminal ileum were red and thickened and the serosa dull and opaque, and covered with plastic exudate. Many large mesenteric glands were seen. Gland was excised and reported as hyperplastic lymphadenitis. The appendix was reported as chronic atrophic appendicitis. He was readmitted to that institution in January, 1930, with a history of pain in the lower abdomen, repeated vomiting and obstipation for two days. A diagnosis of fibrosis of the terminal ileum causing intestinal obstruction was made and the patient was subjected to a laparotomy. The terminal ileum was found narrowed and fixed by numerous adhesions. An ileo-transverse colostomy was performed without division and exclusion of the loop. The patient did not do well after operation and continued to have increasing abdominal colic and marked loss of weight.

When he was admitted to Mount Sinai Hospital in June, 1930, patient was emaciated and visible peristalsis was noted in the lower abdomen. Repeated studies with barium meal and enema failed to cast much light upon the condition in the abdomen. It was thought that the symptoms were due to entrapment of intestinal contents between the site of the ileocolostomy and the stricture in the terminal ileum. With this diagnosis patient was subjected to a laparotomy which revealed an exceedingly complicated series of conditions. Near the site of the old ileo-colic anastomosis a small abscess was encountered, penetrating into the transverse mesocolon. Exploration revealed this to be due to a perforation of a piece of toothpick through the small intestine with considerable degree of stenosis and kinking at this point. As it was impossible to close the perforation about six inches of the small intestine were resected and an end-to-end anastomosis performed. Following this, further exploration revealed that the terminal ileum distal to the anastomosis and the transverse colon were the seat of chronic inflammatory disease. A rapid resection of the terminal ileum, cecum colon, ascending colon and transverse colon to a point distal to the old ileo-colic anastomosis was undertaken and a new ileo-colostomy performed. Patient did remarkably well after this procedure and was discharged greatly improved seven weeks later. Patient has been followed for the past year, has gained forty pounds in weight, and aside from a small sinus communicating with the closed end of the transverse colon, showed no symptoms.

Pathological findings. — The macroscopic specimen consists of a resected portion of the terminal ileum, ileo-cecal junction, cecum, and ascending colon, and a portion of the ileum which has been anastomosed with the transverse colon at previous ileo-colostomy. The terminal ileum is markedly dilated to a circumference of 10 cm. and contains several small serpiginous ulcerations. The ileo-cecal junction is markedly stenosed and barely admits a medium sized probe. The stenosis is due to a large proliferating polypoid mucosal mass overlying the junction and surrounded by numerous ulcerations. The ascending colon, from the ileo-cecal junction to the old ileocolostomy is normal. At this point the mucosa on both sides of the anastomosis is found hypertrophic with numerous ulcerations and small polyps. The lymph nodes in the mesentery are enlarged and hypertrophic. In addition, there is a separate portion of resected small intestine at the center of which there is a perforation in the vicinity of which the wall of the bowel shows marked thickening, fibrosis and annular narrowing. Microscopic examination shows ulceration of the mucosa of acute and chronic suppuration. The walls of the gut are infiltrated with numerous large and small lymphocytes and plasma cells. There are a few eosinophiles and polymorphonuclear leucocytes. There is extensive fibrosis involving all the coats, most marked in the submucosa and the muscularis. No evidence of tuberculosis or amebae disease.

Diagnosis. — Ileo-cecal stenosis due to polypoid ulcerative non-specific ileitis involving the terminal ileum and transverse colon.

10. Operation for supposed appendix abscess. Appendix not badly diseased. Development of fistula in right lower quadrant eight months later. Diseased terminal ileum at operation three years later, for intractable fistulae.

H. C., age twenty-eight, first admitted to the Mount Sinai Hospital in January, 1928. At that time he complained of colicky pains in the abdomen, unrelated to meals of three weeks' duration. The morning before admission, the pain became more severe and was referred to the lower abdomen, especially on the right side. There had been no vomiting, or chills. Temperature had not been taken.

On admission, temperature was 104. Blood count was 20,000 with 92 per cent polys. There was tenderness, rigidity and a mass in the right lower quadrant. Clinically the case was considered a case of appendix abscess. Laparotomy was performed and a large mass, the size of a large grapefruit was found in the iliac fossa. After packing off the intestinal contents, the mass was unraveled and found to consist of the cecum, appendix, terminal ileum and its mesentery and a loop of sigmoid. The appendix was lying in a bed in the mesentery of the terminal ileum, which was about two inches thick and oozing pus. The appendix was removed and rubber-dam drain led down to the necrotic tissue. Aside from a wound infection, patient did well and was discharged one month later. Pathological report of the appendix was acute and chronic inflammation.

Patient was readmitted to the hospital in May, 1931. He had been well for eight months after the operation at which time the scar broke down in one place and for two months drained greyish, odorless fluid and then closed spontaneously. For the next one and one-half years, patient had no symptoms. Two weeks before the second admission he began to experience pain at the site of his scar, which gradually became more severe. On admission, patient's temperature was 103, and beneath the scar a fluctuant mass was present. Upon incision, about 1 ounce of thick, yellowish pus was evacuated. From this abscess cavity a tract led down toward the abdomen. Tube drainage was instituted. Patient drained feces for several days, and lipiodol injected into the wound seemed to run into the cecum. After about ten days the fecal discharge ceased and the wound began to granulate. Barium enema at this time revealed no abnormality in the cecum.

The patient was seen again in July, 1931, at which time, an exudate was still present in, the right lower quadrant. Conservative therapy was continued until November, when an exploratory laparotomy was undertaken. At operation, the terminal 2 feet of ileum were found to be greatly thickened, edematous, hyperplastic and in one of the loops was found, the inner opening of the fistulous tract. It was recognized that the fistula was not of appendicular or cecal origin but probably had at its base, a non-specific ileitis. Accordingly, resection of the $2^1/_2$ feet of terminal ileum, cecum and part of the ascending colon was undertaken and an ileo-transverse colostomy performed.

Pathological findings. — The specimen consists of 40 cm. of terminal ileum, 12 cm. of large bowel and attached skin. From the skin a fistulous tract leading to a point in the ileum, 4 cm. from the ileo-cecal junction. There are some enlarged, moderately firm glands in the ileo-cecal angle. Examination of the interior of the specimen shows cecum and colon to be normal. Beginning at the ileo-cecal valve and extending proximately for 30 cm. there are marked mucosal alterations. The mucosa is markedly thickened, congested and thrown up with irregular folds. Rugae have lost their identity. The surface presents numerous hemorrhages, erosions and ulcerations interspersed with areas of mucosal hyperplasia. Lymph follicles are enlarged. The submucous layer is moderately thickened and fibrotic.

Microscopic examination. — Marked mucosal ulceration with acute-chronic purulent inflammation. Diffuse thickening of all layers of the gut, especially the submucosa, due to edema, granulation tissue and diffuse infiltration with large and small lymphocyte, plasma cells and occasional polynuclear leucocytes. No tubercles or tubercle bacilli seen.

Pathological diagnosis. — Hyperplastic chronic ulcerative inflammation of the ileum.

IV

Localized Hypertrophic Colitis

In addition to a purely localized definitely palpable inflammatory colonic mass, some of these cases at one time or another presented evidence of a low-grade general colitis, much milder in type than the ordinary severe, diffuse ulcerative form. In others, the disease remained localized. That ulcerative colitis may affect predominantly or almost exclusively certain segments of gut has been emphasized by Dr. Berg for years, and recently, Bargen has reported a series of cases illustrating the same point. In most of the present cases there were no roentgenological or sigmoidoscopic evidence of generalized colitis at the time of operation, and the symptoms were attributed entirely to the localized colonic disease. In a few of these cases, persistence of symptoms after resection led to renewed investigation, which in some instances showed evidences of mild colitis, which responded to medical therapy. In those cases where definite evidence of colitis involving other portions of the colon could be shown, coincident with the presence of a mass, it was sometimes possible to obtain a good result by a short-circuiting entero-colostomy. In only one case did definite symptoms appear first in a segment of gut other than in which the hypertrophic mass ultimately developed (case 11).

The cecum and ascending colon were the seat of the disease five times; the recto-sigmoid, three times; the mid-sigmoid, once; and the junction of the sigmoid and the descending colon, three times. In the right colon, the disease usually extended upward until a few inches from the hepatic flexure. The mucosa showed, at times, large irregular ulcerative areas up to $^1/_2$ inch in diameter with areas of hypertrophic mucosa in between them. In other cases the ulcers were smaller and were overshadowed by the bullous polypoid mucosa. Papillomatous and polypoid changes were common in the mucosa. The submucosa was moderately thickened and edematous. The serosa was opaque, and there was marked thickening and hypertrophy of the subserosal fat both in the gut and meso-colon. Glands in the ileo-cecal angle were enlarged. Numerous adhesions to the omentum and surrounding loops of gut were found at operation.

In the sigmoid, the pathological changes were more of a fibrostenotic nature with narrower limits of involvement and relatively little ulceration and with more tendency to stricturing and papillary proliferation in the mucosa. Microscopically the picture was simply that of various stages of inflammatory disease. In addition to tuberculosis, careful search was made in these cases for amoebae. Evidences of neither were found.

Most of these patients had been sick for about six months when they appeared for operation. Abdominal pain, diarrhoea and bloody stools were the most common complaints in the right-sided lesions. When the sigmoid was involved, constipation and painful defecation were present. At times, the symptoms were mainly obstructive. A palpable mass was found either by abdominal examination or in the cul-de-sac by pelvic examination in every case. X-ray showed either an irregular filling defect or an area of narrowing in the involved segment. When the filling defect was unusually extensive, the presence of inflammatory rather than neoplastic disease was suggested. In two cases, radiological evidence of coexisting colitis, in addition to the presence of a local lesion, could be shown. By and large, however, radiological differentiation from neoplasm or tuberculosis was not possible with certainty. The sigmoidoscope is of value in diagnosis not only for removing specimens for microscopic examination but also for demonstrating multiple foci of disease.

At operation, the determination of the exact nature of the pathological changes is again very difficult. Most of these cases were resected under the operative diagnosis of carcinoma or tuberculosis. Ulceration on the inside of the bowel, projection of papillary growths into the lumen and the presence of annular infiltration mimic neoplasm very closely.

On the right side, ileo-colic resection was performed five times with no mortality; no other procedure being adopted for this form of the disease. One of these patients had a mild recurrence of symptoms which cleared up under dietetic treatment.

In the lesions involving the upper and mid-sigmoid, a Mikulicz operation was performed three times, and an exclusion anastomosis to the lower-most point of the pelvic colon once. In another case, where definite evidence of generalized colitis could be demonstrated, in addition to a recto-sigmoid mass, a cecostomy was performed. Marked subsidence in the size of the mass, and diminution in the severity of the symptoms followed. In two localized lesions at the recto-sigmoid junction, abdomino-perineal resection with restitution of continuity by an extra-peritoneal presacral anastomosis was performed according to the technique of Dr. A. A. Berg. The only alternative in these cases would have been a left inguinal colostomy which would probably have resulted in a stricture of the bowel below that site and prevented any attempt at closure of the inguinal anus without a secondary and more difficult resection of the involved area. There were no mortalities in this left-sided group.

11. A patient in whom the development of an inflammatory mass in the cecal region was preceded by a three-year history of intractable perianal inflammations. A period of recovery following resection of the inflammatory mass was followed in a few years by extension of the inflammatory condition to the adjacent distal segment of the colon.

I. F., age forty-four, admitted to the Mount Sinai Hospital for the first time in 1927 with a history of vague abdominal symptoms, and a history of recurrent peri-anal abscesses and fistulae. Examination at this time revealed a number of perianal ulcers and superficial fistulae. Sigmoidoscopy showed a congested mucous membrane covered with shreds of mucus. Stool was negative for blood. Ewald test meal showed an anacidity but neutral red appeared in the gastric contents following injection. Wassermann was negative. Physical examination revealed no other abnormalities.

Following this, there were a series of readmissions for intractable peri-anal ulcers and fistulae and fissures which proved recalcitrant to the ordinary operative measures. Tuberculosis was suspected but the excised specimen proved negative. Three years following his first admission, he was readmitted to the hospital with a history of peri-umbilical and right lower-quadrant pain of four months' duration. He had occasional periods of diarrhea, but in between his bowels were normal. On one occasion, he passed a moderate amount of bright red blood in his stool.

Physical examination showed a man, chronically ill, and moderately anemic (hemoglobin 68 per cent). In the right lower quadrant, a firm mass, about the size of a small grapefruit, was palpable. It was fairly fixed. Sigmoidoscopy revealed no abnormalities. Barium enema revealed a marked and constant irregularity and filling defect involving the cecum and ascending colon. The findings were considered suggestive of an intrinsic lesion, probably neoplasm.

Patient was operated upon under the preoperative diagnosis of either neoplasm or hypertrophic tuberculosis of the colon. At operation, a large mass, involving the cecum and the ascending colon was discovered to which there were numerous adhesions of omentum and transverse colon. An ileo-colic resection was performed.

Pathological report. — Macroscopic specimen consists of the resected portion of the cecum and ascending colon together with the appendix and small portion of the ileum. Cecum is very definitely thickened and narrowed by an inflammatory process beginning at the ileo-cecal junction and extending upward for 12 cm. This portion of the cecum shows a large, irregular ulcerative process, finely granular and red with numerous interspersed areas which have the appearance of hypertrophic granulations plus hypertrophic mucosa. Around the margins, of the ulcerated area, mucous membranes show a polypoid hypertrophy. Jutting out from this main area are numerous finger-like ulcerative areas surrounded by hypertrophic mucous membranes. The appendix is apparently involved in the inflammatory process. It is red and infiltrated and through its intestinal orifice there is a projection of polypoid mucosa. The distal 4 cm. of the ascending colon, in contrast to the remaining portion, is smooth, pale and atrophic. Numerous shotty lymph nodes are found in the meso-colon, appearing grossly hyperplastic. Cultures from the bowel show enterococci and colon bacilli. Guinea pig, rabbit and chicken inoculations for tuberculosis are negative.

Histological examination. — Showed acute and chronic inflammation. There are no evidences of tubercle or caseation necrosis.

Diagnosis. — Non-specific inflammatory disease of the cecum and the ascending colon.

Following operation, patient did well for about two years; he gained weight and his peri-anal ulcers healed. Recently he commenced to lose ground again. X-ray at the present time shows an apparent extension of the same type of inflammatory lesion previously present in the cecum, to the distal transverse colon.

12. Case of localized ulcerative colitis

I. L., age fifty-five, admitted to the Mount Sinai Hospital in 1924. The chief complaint was pain in the right lower quadrant and diarrhea of four months' duration. Pain in the right lower quadrant was dull and gnawing, frequently started after meals and continued for one-half to one hour. Bowels moved six to seven times a day. Occasionally they were tarry. Five weeks before admission, a mass became palpable in the right lower quadrant.

The appendix had been removed seventeen years previously.

Physical examination showed a man, chronically ill, apparently having lost considerable weight. The abdomen was slightly distended and in the right lower quadrant, a mass, the size of an orange, slightly tender, and slightly movable, could be palpated. Hemoglobin was 88 per cent. Wassermann was negative, stool contained small quantities of blood. X-ray showed a filling defect in the cecum and ascending colon. The rest of the colon appeared normal. Preoperative diagnosis of carcinoma of the cecum was made, and an ileo-colic resection performed.

Pathological examination. — Specimen consisted of about 10 cm. of cecum and 18 cm. of ascending colon. Colon and ileo-cecal angle were covered with a large amount of hyperplastic fat, almost obscuring the peritoneal covering. Where the peritoneum was visible, particularly over the ileum, there were small peritoneal nodules, suggestive of miliary tubercles or lymphoid infiltration in fatty deposits. On section, the ascending colon down to the cecum was the seat of an ulcerative colitis with polypoid infiltration. The very terminal portion of the ileum also showed evidence of superficial erosion.

Histological sections showed simply various grades of acute and chronic non-specific inflammation. No evidence of tuberculosis or amebiasis could be found.

Following operation, patient developed a small fistula and continued to have diarrhea. This persisted for about six months when the diarrheal symptoms disappeared, and the fistula closed spontaneously. This patient has been observed in the Gastrointestinal Clinic of the Mount Sinai Hospital for the last seven years and has been noted to have occasional flare-ups of low-grade colitis, which at times could be seen to involve the lower sigmoid segment. His general condition is good.

13. Case of localized hypertrophic colitis. Fistula following previous appendectomy

A. S., age twenty-three, admitted to the Mount Sinai Hospital in 1929, complaining of severe cramps and diarrhea of three weeks' duration. The pain was increased after ingestion of food. Stool varied in consistency from liquid to mushy but contained no blood or pus.

Physical examination revealed a tender mass in the right lower quadrant. At this time the hemoglobin was 85 per cent and the white blood count was 23,000 with 81 per cent polys. Temperature varied between 100 and 101 degrees. Examination of the stool showed some pus; no parasites, ova, or amebae. Course of emetin had no effect. X-ray following barium enema showed a defect involving the cecum and ascending colon. Barium meal showed the same picture. Chest x-ray was negative.

Exploratory laparotomy revealed cecum and ascending colon to be rather thick and injected. No evidence of tuberculosis could be seen in the external covering of the bowel. No definite ulcerations were palpable inside the bowel. Appendix was removed and the patient was discharged.

Two months later he was readmitted with a loss of weight, continued diarrhea and persistent fistula in the right lower quadrant. Stools were negative for tubercle bacilli, actinomycosis and amebae. Another course of emetin was given without avail. One month later, as symptoms persisted, exploratory laparotomy was performed and ileo-colic resection plus an ileosigmoidostomy was performed.

Pathological description. — Macroscopic specimen consisted of cecum, ascending colon and a small portion of the terminal ileum. The mucosa of the colon showed marked edematous polypoid hyperplasia giving the mucosa a cobblestone appearance. Between the polypoid projections were occasional, irregular small ulcerations. There were a few papillary mucosal projections. Peri-intestinal lymph nodes appear hyperplastic. There does not seem to be much involvement of the deeper layers of the gut, except for an inflammatory edema.

Microscopic examination showed areas of ulceration in the mucosa with hemorrhagic and acute and chronic purulent inflammation. At other points the mucosa was hyperplastic. The submucosa showed mainly edema with round-cell infiltration. The muscularis was thickened and showed moderate fibrosis. There were no evidences of tubercle bacilli or anatomical tubercles. No amoebae seen on section.

Pathological diagnosis. — Non-specific ulcerative colitis and polyposis.

Patient made uneventful recovery and has remained well to date.

14. Localized hypertrophic sigmoiditis and peri-sigmoiditis with diarrhea and bloody stools

R. H., age 27, admitted to the Mount Sinai Hospital in September, 1922. Chief complaint was diarrhea of two years' duration. She had six to seven movements per day, and the stool frequently contained fresh blood. At times, there was severe cramp-like pain. She had lost 15 pounds in the past year. Red blood count was 3,500,000. Hemoglobin was 35 per cent. Stool showed fresh blood; no amebae, ova or parasites.

A mass was palpable in the left lower quadrant. Sigmoidoscopy showed an ulcerative infiltration 15 cm. from the anus, mainly on the anterior and right lateral wall. A specimen removed was reported as chronic inflammatory tissue. The fresh secretion was examined for amebae but none found. An appendicostomy was performed and the cecum was reported as being hard and indurated as though the seat of chronic inflammation. Patient was given a course of emetin and irrigation was performed through the cecostomy. Barium enema showed a narrowing of the sigmoid and a filling defect in the region of the descending colon and sigmoid. The rest of the colon appeared normal. Sigmoidoscopy again showed a granular infiltrating mass which the sigmoidoscopist considered carcinoma, but which was reported as inflammatory tissue. The mass in the left lower quadrant became larger and patient showed no signs of improvement.

At the second operation, a large mass, the size of a grapefruit, densely adherent to the latero-pelvic wall and surrounded by firm adhesions was found. Resection was performed.

Pathological examination. — Macroscopic specimen consisted of resected sigmoid about 20 cm. in length, showing a tremendous productive inflammatory process, infiltrating its wall, constricting the lumen and involving peri-sigmoid tissue. The mucous membranes showed a rather polypoid appearance with marked thickening of the sub-mucosa, apparently inflammatory in nature, and without ulceration or diverticula. In the center of the specimen where the inflammatory process was most marked there seemed to be a necrosis of the intestinal wall.

Microscopic examination showed acute and chronic inflammation. No signs. of neoplasm or tuberculosis. Pathological diagnosis: Chronic and acute sigmoiditis and peri-sigmoiditis.

15. Hypertrophic colitis (sigmoid) with gradually increasing obstructive signs

H. B., age 67, admitted to the Mount Sinai Hospital in May, 1926. Chief complaint was gradually, and markedly increasing constipation of a few months' duration. There had been occasional appearance of blood in the stool. One month before admission, barium enema showed a constriction with an incomplete but fairly tight obstruction at the junction of the descending colon and sigmoid, approximately at the level of the brim of the true pelvis. The appearance of the descending colon, judged by the barium in it after evacuation suggested colitis. At this time, a mass could be felt in the left lower quadrant. Since the x-ray had been taken patient had become gradually more obstipated, until upon admission he was passing only small quantities of gas.

Because of the increasing obstruction, it was felt advisable to resect or short-circuit the mass, regardless of its nature. At operation, a mass, 3 inches long, densely indurated, and very adherent to the parietes was found and a Mikulicz operation performed.

Pathological report. — Hypertrophic colitis. No signs of malignancy. No diverticula found.

The artificial anus was later closed, and when last heard from two years after operation, the patient was feeling well.

16. Localized inflammatory annular stricture with polypoid hypertrophy of mucous membrane just above recto-sigmoid junction

F. S., age 53, admitted to the Mount Sinai Hospital in June, 1925. She had been sick for a year, with increasing constipation and rectal bleeding. The severity of both symptoms had increased considerably, just before admission. On examination a mass could be felt in the left iliac region. X-ray showed a stricture at the recto-sigmoid junction. Proctoscopy showed no abnormality in the lower rectum, and a stricture was encountered at the recto-sigmoid junction.

Because of the increasing symptoms, it was decided to operate in spite of the fact that the exact nature of the lesion could not be definitely determined. It was felt that a colostomy would simply result in the production of a complete stricture if the lesion were benign. It was, therefore, decided to resect the involved lesion, which was done according to the technique of Dr. A. A. Berg by abdomino-sacral excision with restitution of continuity by end to end extra-peritoneal pre-sacral anastomosis.

Pathological description. — Macroscopic specimen consists of resected portion of sigmoid 10 cm. in length containing an annular lesion 5 cm. in diameter, causing constriction at that site. There is a marked polypoid hypertrophy of the mucous membrane in this region. The muscular wall of the bowel above the lesion is thickened. The lymph nodes are slightly enlarged. Microscopic examination shows polypoid hyperplasia of the mucosa, diffuse fibrosis and round cell infiltration of the rest of the wall of the sigmoid.

This patient was readmitted about six months later for dilatation of stricture developing at the site of the anastomosis. Following this procedure, patient has remained well to date.

V

Simple Penetrating Ulcers of the Colon

This term is applied to a group of cases which show one or more clean-cut penetrating ulcers which look almost like punched out peptic ulcers. It is apparently a purely local disease; the surrounding colon not appearing to be grossly diseased. In two cases, penetration had occurred through the colonic wall and had become sealed off by adhesions of omentum or epiploic appendices, with the formation of rather firm inflammatory masses, which gave the impression of being penetrating or perforating neoplasms. Both these lesions were situated in the ascending colon and, clinically, were operated upon with diagnoses of acute appendicitis. At operation they were mistaken for carcinoma of the colon and were resected as such.

Another patient, who probably belongs in this group is one who developed signs of incomplete obstruction in the transverse colon and who, at operation, was found-to have a narrow, inflammatory annular stricture. There were no evidences of disease of other portions of the colon, and the narrow, local, annular stricture can probably be best explained as a result of the healing of a penetrating ulcer.

Another manifestation of the same type of lesion was encountered at autopsy in a patient who had experienced severe repeated hemorrhages from the bowel, one of which finally proved fatal. Twelve cm. from the rectum a group of punched out ulcers was encountered. At the base of one of these was an arteriosclerotic vessel which had been eroded by the penetrating ulcer.

We have no exact idea as to the underlying etiology of these lesions. It is possible that they are due to injuries by ingested foreign bodies. There is also a possibility that they are of vascular origin due to blocking of a small vessel. Some point is lent to this latter view by our experience with a case encountered a few months ago. This latter patient was admitted to the hospital as a perforated duodenal ulcer with x-ray evidence of free air in the diaphragm. Exploration showed, however, that perforation had occurred in the lowermost ileum which contained four sharply punched-out perforations, about 1/2 cm. in diameter. These were sewn up and an ileostomy performed. The patient did well for a few days, then suddenly went into collapse, commenced to drain blood through the ileostomy tube, and died shortly thereafter. Autopsy showed a mesenteric thrombosis. The area of ileum where the perforation had occurred was normal except for the sharply punched-out ulcers. Our interpretation of this course of events was that the thrombus had originally been parietal and that small emboli had broken off, plugged some of the terminal arteries or arterioles and given rise to the rapidly perforating ulcers, and that later the parietal thrombus had become complete. These are the only facts which we can adduce, which at all throw any light on the etiology of this type of ulcers.

17. Penetrating ulcers and annular stricture

E. R., age 23, admitted to the Mount Sinai Hospital in December, 1928. For two months she had complained of increasing pain and constipation, borborygmus and occasional blood in the stools. She claimed to have experienced a similar attack one year ago, which lasted for a few weeks and then disappeared.

Physical examination revealed a sausage-shaped mass in the upper abdomen. There was occasional intestinal erection noted. The x-ray revealed an irregular narrowing of the transverse colon for a distance of two inches.

Laparotomy revealed a stenosing lesion of the colon, annular in nature, in the middle of the transverse colon. Resection with side to side anastomosis was performed.

Pathological examination. — Specimen consists of a portion of resected transverse colon 7 cm. in length, which was divided into two portions by a narrow linear stricture approximately 1 cm. wide which presents small nodular elevations in mucosa and a small polyp as well as several small irregular ulcerations. The gut proximal to this area is dilated to approximately twice the circumference of a normal bowel and the thickness of the wall approximately twice that of normal.

Microscopic examination showed acute and chronic inflammation. No evidence of malignancy or tuberculosis.

Pathological diagnosis. — Ulcerative stricture of the colon, non-specific in character.

VI

Inflammatory Masses Secondary to Appendages of the Bowel (Appendicitis, Typhlitis, Diverticulitis)

Probably the best known type of this variety of inflammatory mass is that which is secondary to sigmoid diverticulitis. These have been so much discussed in recent years that we feel there is no reason for including them in the present study. We wish, however, to emphasize in passing, that in addition to the large peri-sigmoidal inflammatory masses caused by perforation of a diverticulum or extension through it of infection from the lumen of the bowel there is another and less common type. In this, there is a gradually developing submucous infiltration of the sigmoid as well as an adherent peri-sigmoiditis, with the development of a considerable degree of intramural fibrosis and hyperplasia and a considerable degree of stenosis. This type is clinically and radiologically extremely difficult to differentiate from malignant stenosing lesions of the sigmoid and even at operation, differentiation may be impossible.

The relation of the appendix to the development of certain hypertrophic masses in the ileo-cecal region is a moot point. In many cases an unresolved appendicitis is undoubtedly responsible for the formation of a hyperplastic fibrotic mass, the so-called "appendicitis fibroplastica," but this does not account for all the lesions found in this region. In these cases, the appendix is found buried in the cecal wall or as in one case of this series, in the terminal ileum; and forms part and parcel of the inflammatory mass. The extension of the inflammation in these cases is simply by contiguity and as might be expected is mainly peri-cecal with involvement of the sub-serosal tissue. The submucous layer of the gut does not appear to be involved. Occasionally tiny abscesses between the appendix and the cecum will be uncovered when the former is mobilized. These are quite common, their true nature is usually appreciated and resection is rarely performed.

There is another, and much rarer type of lesion, however, which may he called chronic typhlitis, in which the appendix though thickened and indurated lies free and non-adherent.

Both it and the cecum show a marked submucous thickening, edema and fibrosis. The lesion does not extend up into the ascending colon or into the ileum except at the ileo-cecal valve, points which serve to differentiate it from the two other types of non-specific inflammatory disease encountered in this region, which have been discussed above. Large masses of firm glands are found in the ileocecal angle. Upon examination, the pathological alterations involving the appendix and cecum are seen to be continuous. If the route of spread were by direct extension, it would have to be through the contiguous submucous layers of the appendix and cecum. However, from the clinical standpoint, it is well known that inflammation of the appendix usually stops short of the extreme base even in the most virulent form of the disease. Dr. Klemperer, who was at one time greatly interested in the extent of the basal involvement in acute appendicitis, was able to substantiate our clinical observation from his pathological studies.

The question then arises as to whether the extension is into the cecum from some unusual form of acute appendicitis involving the base, or whether the ileo-cecal changes were primary, the appendix participating simply as a component portion of this segment of gut. We are inclined to believe that the type of chronic cecitis with extensive submucous-intramural involvement, but without evidences of mucosal ulceration is secondary to a partially resolved acute or chronic typhlitis.

There is no doubt about the existence of acute typhlitis as a clinical entity. On an active emergency service three or four such cases are encountered every year. Clinically and on physical examination they present the picture of acute appendicitis. Operation, however, reveals a succulent edematous, inflammatory lesion without much peritoneal injection or fibrin deposition. involving the cecum, the retro-peritoneal tissue, the appendix, and the ileocecal glands. The appendix does not appear to be more acutely involved than any of the adjacent tissues. In some of these cases, the appendix and a lymph gland from the ileo-cecal angle were removed. On pathological examination these revealed only acute inflammatory hyperplasia. In one subacute case, where ileocecal resection was performed, a small ulcer was still present in the cecum. The submucosal proliferative reaction was all out of proportion to the size of the ulcerative lesion. Most of these acute cases clear up, probably, either with or without operation. An especially severe case was recently encountered which came to post-mortem examination. The cecum was found greenish-black and gangrenous. There were numerous cecal ulcerations, two of which had gone on to perforation. The appendix was gangrenous. Jennings has recently called attention to this type of case.

In other cases, repeated attacks finally result in the formation of a chronic submucous and subserosal inflammatory infiltration. In these chronic cases, there are no ulcerative, polypoid or papillary changes in the mucosa; the glands are firm; the cecal wall thickened and indurated, and there are few adhesions present.

The symptom usually complained of is recurrent attacks of pain in the right lower quadrant without any history of blood in the stool, diarrhea or constipation. At times, the chief complaint is that of a mass. Radiologically, filling defects or irregularities in the cecum are present. The general condition is usually good, operation being mainly undertaken because of the presence of a mass. At operation, differentiation from tuberculosis may be difficult and most of the cases subjected to resection have been operated because of their similarity to that condition.

19. Peri-typhlitis. A case of so-called appendicitis fibro-plastica chronic productive peri-appendiceal inflammation leading to the formation of a large mass

L. K., age 18, was admitted to the Mount Sinai Hospital in October, 1929. For $2^1/_2$ months he had been suffering recurrent attacks of pain in the lower abdomen. Two days before admission, an especially severe attack had begun in the lower abdomen and had finally localized to the right side. There was nausea, but no vomiting. Examination showed tenderness and rigidity in the right lower quadrant. Preoperative diagnosis was acute appendicitis.

At operation the entire ileo-cecal region was found to be involved in a moderate sized, hard, stony mass which infiltrated the cecal wall. The ileo-cecal angle contained numerous glands of the same stony hardness. The appendix could not be visualized and seemed to be part of the large conglomerate mass. After considerable debate, an ileo-colic resection was performed.

Pathological examination. — Specimen consists of terminal ileum, cecum and part of the ascending colon. There is no intrinsic lesion of the mucosa of any of the resected bowel. In the ileo-cecal angle, surrounding the appendix and involving the terminal mesentery, is a chronic inflammatory mass of tissue including a large number of hyperplastic lymph nodes. The appendix, 7 cm. in length, appears to be chronically inflamed and stenosed, particularly in its distal two-thirds.

Microscopic examination showed a marked fibrosis of the appendix involving all the coats with a marked lymphocytic infiltration. The cecum simply showed chronic peri-typhlitis.

Diagnosis. — Chronic appendicitis and peri-typhlitis.

20. Case of chronic productive typhlitis resembling tuberculosis

A. B., age 35, admitted to Mount Sinai Hospital in March, 1930. One year ago patient had a severe attack of pain in the right lower quadrant which persisted for two weeks. She had no generalized abdominal pain at that time, no vomiting. She believes she had fever. Five days before admission she again developed pain in the right lower quadrant with rather marked severity, much more so than the occasional dull pain which she had been experiencing in the interval. She had no diarrhea or blood in the stool. There had been no increasing constipation or loss of weight. Physical examination revealed a mass, the size of an orange, in the right lower quadrant, rather firm, slightly irregular. The preoperative diagnosis was appendix abscess.

Exploring revealed a mass occupying the ileo-cecal region covered by thickened omentum. When the omentum was separated the appendix was found lying free and did not appear acutely inflamed. There was a marked infiltration of the ileo-cecal angle and cecum. It was thought that the lesion might be a hypertrophic tuberculosis and an ileo-cecal resection was performed.

Pathological description. — Specimen consists of terminal ileum, cecum and ascending colon. The region of the entrance of the ileum into the cecum appears firm, nodular and edematous. Upon opening the specimen the mucosa of the resected bowel appears grossly normal except for some edema of the ileo-cecal valve and the caput-coli. The mesentery of the ileocecal junction appears firm, and infiltrated and on section seems to contain some succulent lymph nodes, surrounded by firm, hard, inflammatory tissue. The appendix was not adherent and appears moderately thickened. An inflammatory mass extends from the mesentery of the ileo-cecal junction and appears to involve the wall of the cecum. It is firm and irregular. On section of this area, the cecum appears to be markedly thickened, shows edema and infiltration of all the coats, especially the submucosa. Microscopic examination shows diffuse infiltration of the submucosa with round cells and with considerable edema. There is a moderate amount of fibrosis. There is a considerable thickening and edema of the serous coat as well as the mesentery. The appendix shows signs of chronic inflammation, fibrosis, but little inflammatory infiltration.

Diagnosis. — Chronic typhlitis, peri-typhlitis, chronic appendicitis.

21. Subacute, ulcerative and phlegmonous typhlitis

D. W., age 31. Was admitted to the Mount Sinai Hospital in March, 1930. He had been ill for two days with peri-umbilical pain and nausea. He had had two similar previous attacks, which were supposed to be due to appendicitis. Previous history was negative except for respiratory symptoms coming on during the winter. Examination showed slight tenderness and rigidity in the right lower quadrant; temperature was 101, and leucocyte count was 12,000 with 80 per cent polys. At times it was thought that a mass could be palpated in the right lower quadrant, but this could not be established with certainty. X-ray of the chest showed a chronic pulmonary phthisis.

At operation, which was undertaken with the preoperative diagnosis of appendicitis, the appendix was found to be normal, but there was a tumor in the cecum about the size of a pigeon's egg. An ileo-colic resection was performed.

Pathological examination. — Specimen consists of cecum, appendix 12 cm. of ileum, and a few cm. of the ascending colon. The ileum shows no gross lesion. The appendix shows some external signs of inflammation in the distal third. In the cecum, near the base of the appendix, but not involving it, there is an extensive ulcerative, necrotizing inflammation over an area about 3 cm. in diameter, with a gangrenous membrane about 2 cm. in diameter, and minute ulcerated areas covered with a yellowish sloughing base. The wall of the cecum is much thickened, the serosa inflamed. Regional lymph nodes are enlarged. Aside from this area, the cecum appears normal as does the ascending colon.

Microscopic examination. — The ulcerated area shows necrosis of mucous membranes with a diffuse purulent infiltration consisting of lymphocytes and polymorphonuclears through all the coats of the gut. There is considerable edema, small areas of hemorrhage extravasation. The ileum and ascending colon are normal. The appendix shows some slight increase in the submucosa, some injection of the serosa, but no signs of intrinsic inflammatory changes.

Diagnosis. — Ulcerative and phlegmonous inflammation of the cecum.

Summary

1. A study is reported, fifty-two cases exclusive of sigmoid diverticulitis manifesting themselves as tumors or strictures of the bowel.

2. Clinically, radiologically, and at operation these were usually regarded as malignancy or localized hypertrophic tuberculosis.

3. Microscopic examination of these resected specimens showed various stages and degrees of acute and chronic inflammation with the production of large quantities of fibroblastic and fibrous tissue.

4. No exact pathological or etiological classification is attempted. For clinical purposes they are divided into six groups, some of which are overlapping. 1. Peri-colonic or peri-intestinal granulomata due to sealed-off perforation. 2. Intestinal stenosis due to known vascular lesions of the bowel. 3. Localized hypertrophic ulcerative ileitis. 4. Localized hypertrophic colitis. 5. Local penetrating ulcers of the colon. 6. Granulomata secondary to inflammation of appendages, or diverticula of the bowel.

5. The various groups are discussed and illustrative cases briefly reported.

6. Localized hypertrophic tuberculosis of the bowel in patients without evidence of pulmonary tuberculosis, is less common at the Mount Sinai Hospital than the non-specific variety.

The authors are greatly indebted to Dr. A. A. Berg for so generously placing his extensive material at their disposal. To Dr. Paul Klemperer they wish to express their appreciation and thanks for his patience and kindness in aiding them in the study of the pathological phases embodied in this communication. To Drs. Harold Neuhof, Edwin Beer and Richard Lewisohn, Dr. I. C. Rubin and Dr. Maurice Rashbaum they are indebted for the use of individual cases.

Discussion

DR. GEORGE MORRIS PIERSOL: I can think of no one more fit to discuss the subject of Intestinal Tuberculosis than Dr. Lawrason Brown, who has had a tremendous experience with this condition. He was speaking, of course, of secondary intestinal tuberculosis. The importance of this subject to the clinician must be obvious when one considers, as Dr. Brown has already remarked, that it is the most common complication of pulmonary tuberculosis. Autopsies indicate, I believe, that over 50 per cent of cases of pulmonary tuberculosis exhibit some evidence of intestinal tuberculosis.

In the past the great difficulty has been that the diagnosis of intestinal tuberculosis was never arrived at sufficiently early to make it possible really to do anything for the condition. The reason for this was that the diagnostic methods available were inadequate and clinicians acquired the habit of looking for what were regarded as the classical signs of this condition which in reality were terminal or late manifestations. Such symptoms as pain or localized signs in the abdomen, and the appearance of blood and pus in the stools were looked upon as the criteria necessary to make the diagnoses of intestinal tuberculosis. Dr. Brown and his associates when they recognized the x-ray manifestations of intestinal tuberculosis made a noteworthy advance in the early diagnosis of this condition. Since this method of diagnosis has been generally adopted many cases have been recognized sufficiently early to do something for them. We must all acknowledge the debt which we owe to Dr. Brown and his associates for having pointed out this important aspect of the subject.

Frequently the finding of tubercle bacilli in the stools has been looked upon as evidence of intestinal tuberculosis. In this connection it is important to remember that many times tuberculous individuals swallow their sputum so that the tubercle bacilli are found in the stools without intestinal tuberculosis being present. Therefore, the mere finding of the bacillus in the stool is not enough to make the diagnosis.

The cases Dr. Brown discussed were chiefly the usual ulcerative variety. He did not touch upon some of the sequelae which result in these cases. In the last paper, reference was made to certain sequelae found in some of the cases in whom proliferative changes occur in and around the bowel. They present great difficulty in diagnosis and are often mistaken for neoplasms and require surgical intervention. The type of case Dr. Brown discussed is, of course, not surgical. They only become so when, as the result of tuberculous ulcerations, stenoses develop and symptoms of varying degree of intestinal obstruction supervene. That, of course, is another aspect of intestinal tuberculosis that has to be borne in mind and which calls for a different type of therapy. I should like to ask Dr. Brown in conclusion how often they found tuberculous peritonitis in their cases of intestinal tuberculosis.

Dr. Franklin W. White: I am sure the members of this Association realize the great service which Dr. Brown and his co-workers have given in studying this disease and in practically creating this diagnosis. If we look back a dozen years ago when his papers were first published, we find a condition which was very different from today. We find the best clinicians considering the early diagnosis of intestinal tuberculosis as practically impossible, and the evidence of later disease very uncertain. Now Dr. Brown comes here and shows us the figures of his positive diagnoses of 98 per cent accuracy in cases which have been checked up by autopsy and operation. Certainly something has happened in these twelve years, largely due to the work of Dr. Brown and his associates.

He has shown us the great frequency of intestinal tuberculosis in pulmonary cases with indigestion and abdominal symptoms and also the great rarity of intestinal tuberculosis in patients who have no tuberculosis elsewhere. How has this change in diagnosis come about? Not so much, it seems to me, by clinical study. We know that the early symptoms are much like the symptoms of pulmonary tuberculosis, slight, vague and indistinct at first. In our physical examination we do not find much in the abdomen in the early cases. We do not get much that is really helpful from the stools as far as my experience goes. Of course the proctoscope doesn't help us much because it doesn't get up high enough to see the things we are searching for. It seems to me the roentgen-ray has been our mainstay in bringing about this great change to better diagnosis. First, by finding the changes in function which come in the earlier stages of the disease, the spasm, the hypermotility, the vacant irritable areas in the bowels, and later in the more advanced cases by finding the actual deformity of the local lesion itself.

The question of whether to give a barium meal or a barium enema is not an important one, they both have their uses. I have been struck several times with the value of the double contrast enema by giving the ordinary barium enema and after letting the barium run out, inflating the bowel with air, thus bringing out the projection of masses in the wall into the lumen of the bowel. This brings them out much more clearly than the simple enema and takes only ten minutes more to do. Inflate the bowel under the fluoroscope and take an additional film and you have a picture which may show a great deal.

Of course Dr. Brown has not claimed that the x-ray picture was diagnostic in itself, but the presence of irritation and ulceration and the fact that it occurred in certain parts of the bowel, and that it also appeared in patients who had pulmonary tuberculosis makes a very strong combination which leads us to our diagnosis. Dr. Brown has emphasized the importance of finding constant defects, not merely in one examination which might be so misleading in the bowel, but on repeated examination. I was also struck with the changes which he was able to demonstrate by following the same patients over a period of time so that the progress of healing might be studied and followed very much as we do in gastric ulcer.

Dr. H. Bockus: Mr. President and Members of the Society: This paper of Dr. Ginzburg and Dr. Crohn is of decided interest, not because these lesions that they are describing are at all common, but because of their rarity I think we are very apt to overlook them. As far as I know, this series of cases which they are reporting is the largest group of cases of this sort in the literature, although I ran across an article by H. E. Mock in *Surgery, Gynecology and Obstetrics*, written last year who reported a series of cases almost approximating that of Dr. Ginzburg and Dr. Crohn. They mentioned the same etiological factors which were discussed by the essayist here this morning. One of the particular things discussed in the paper mentioned is the fact that many of these cases of so-called inoperable carcinoma reported to have recovered are probably cases of non-specific granulomata. He stressed particularly the necessity for taking biopsy material even in the cases in which inoperable carcinoma seems to be present. I naturally have had very little experience with this condition and consequently, can't add anything particularly to the discussion from the practical standpoint, but there are several questions that I should like to ask.

I happen to have seen a patient within the past two weeks who possibly has a non-specific granuloma, but who certainly has a peri-sigmoiditis, with blood in the stools which followed almost immediately after deep x-ray and radiation therapy for carcinoma of the cervix. There is at present no indication of carcinoma in the pelvis. I am wondering whether in any of these cases Dr. Ginzburg or Dr. Crohn have noted the development of a granuloma following deep radiation or x-ray therapy.

Dr. Ginzburg mentioned the fact that amebic disease can cause this condition and very recently three cases of this sort were reported following a persistent isolated amebic ulcer and in all three of these cases it was only in the resected material in which the ameba could be found. So it is quite possible an amebiasis may account for some cases of non-specific infective granulomata. My experience comprises only two proven cases and interestingly enough, both of these cases occurred in luetic individuals. I don't mean to infer that these people had syphilomata; one was a case of old duodenal ulcer in which the gall bladder, pancreas and stomach were all bound up in a granulomatous mass which was not carcinomatous; the other case, a solitary ulcer of the ascending colon near the hepatic flexure, with a granulomatous mass associated with it.

I should like to say a word about the terminal ileitis, which I have never seen in my own practice. I went up to see the cases at Mount Sinai with Dr. Crohn and I have been thinking a good deal about it since that time. I don't know very much about anatomy, not being a surgeon, so I went out to Dr. Batson, professor of anatomy at the Graduate School, and saw some of his very excellent so-called extra-peritoneal dissections. He dissects the peritoneum away from the fascia so he can throw all the peritoneal contents encapsulated within the peritoneum to one side and inspect the blood supply. He pointed out to me the fact that the ileo-colic artery, ascending branch, which supplies the cecum is more or less fixed in most specimens, but the terminal branch of the same artery which supplies the lower 6 to 12 inches of ileum is capable of a good deal of rotation. We were wondering whether in some individuals with undue ptosis the factor of disturbed circulation might be a contributing factor in the production of terminal ileitis by twisting the artery or by undue stasis in the vein (terminal branch). I should like to ask whether the habitus of these patients that have been described is of the visceroptotic type, the type in which ptosis and stretching of the mesentery is most marked.

Dr. Walter C. Alvarez: In view of the difficulties of early diagnosis of intestinal tuberculosis perhaps the logical thing to do would be to treat every patient with active pulmonary lesions as if he had trouble in the bowel and give him a smooth diet and plenty of vitamins from the start. Some of my friends who specialize in tuberculosis tell me that that is what they are doing, and that they are pleased with the results.

Some writers have stated that the physician can suspect the development of intestinal tuberculosis when the patient who was formerly optimistic becomes anxious and pessimistic. It is generally assumed that disease in the lungs does not produce the reactions on the brain that are produced by disease in the bowel. I haven't enough experience with these patients to say, whether or not this is true but I know any disturbance in the bowel that is associated with nausea is extremely disheartening.

There are good reasons for giving a smooth diet to these patients. If, in a dog, one takes a section of gut, reverses it end for end, and restores the lumen of the bowel with two anastomoses, the bowel looks exactly the way it looked before, with just as good a lumen. The difference is that the reversed loop will pass fluids but not solids. The dogs must be kept on a cellulose-free diet; otherwise they soon die of intestinal obstruction due to the accumulation of a mass of indigestible material immediately above the orad suture line. It is evident that before one can get solids through the digestive tract, one must have a normal downward gradient of forces. An irritant lesion of the bowel tends to reverse the gradient and this makes it hard for indigestible residues to go through.

The lesions that have been described by Dr. Crohn and Dr. Ginzburg interest me. I think I must have seen instances of this disease in the past; granulomas which I thought might be tuberculous but in which I could not find the characteristic histological structure. Unfortunately for the progress of our knowledge in some of these cases, the surgeon does a short-circuiting operation and the patient disappears. One must be careful not to tell these people that they have carcinoma. A prominent surgeon claims the credit for building a beautiful Christian Science Church. In a wealthy woman he found what he thought was an inoperable cancer of the bowel; he short-circuited it and sent her home with a hopeless prognosis. Later, when he had seen more of these lesions he understood why his patient didn't die.

I have long felt that there must be such a thing as terminal ileitis. I think it is a fairly common disease and some day I would like to disappear into a pathological "lab" to hunt for it myself. Ileitis would account for many of the cases of appendicitis in which the patient doesn't get well after one or more operations.

There is a reason why we should expect trouble in the terminal loop of ileum and this is because it is the one place in the bowel in which the gradient appears to be reversed. This, I think, accounts for the fact that all big gall stones that slough through into the bowel stop some 9 or 10 inches orad to the ileocecal sphincter. To explain it, authorities state that this is the narrowest part of the gut. This may or may not be true. For years I have been trying to plan an experiment which would show whether the gall stone stops where it does because this is the narrowest place or because it represents the place where the gradient is reversed. Finally a woman very obligingly performed the experiment that I wanted. She ate bran until she had to be operated on for the removal of a mass of it impacted right at the danger spot. The case was reported recently in the *Journal of the American Medical Association* (Davis, M. B., 97:24-25, July, 1931). This experiment indicates to me that it is not a narrowing of the gut but a reversal of the gradient that causes the trouble. We can see now why fish bones or any other indigestible remainders will tend to stagnate in this region.

Dr. Harlow Brooks: Mr. Chairman and Members of the Society: I think the work which Dr. Gray has done is a very hopeful harbinger for the future. If the gastro-enterologists particularly will pay some more attention to the problems that we internists have and help us more effectively in the study of general disease it will add greatly to our mutual benefit. Then I have been very much interested in the work he has done because for eight years I was pathologist to a large tubercular service which comprised nearly 50 per cent of active cases of tuberculosis. I never saw a tubercular ulcer of the stomach although we found, even by our crude methods of that day, tubercle bacilli present in the mucus of the stomach swallowed from the sputum of the infected lung. The walls of the stomach have no immunity against tubercular infection. I know that because in subacute or even in active miliary tuberculosis the process starts in the peritoneal coat and through to the mucosa in quite frequent instances. All of you may confirm that by simply doing autopsies in miliary tuberculosis, particularly in the subacute type. On the other hand, in a very large number of active cases of tuberculosis which I saw in my medical youth, I never saw a tubercular ulcer originating from the mucosa of the stomach. I saw two instances which I thought might be of this nature, but when we examined these two ulcers histologically they were prepyloric ulcers and of the typical peptic ulcer type. We carefully examined the edges of these ulcers and I fully expected to be able to demonstrate the formation of tubercles, but that we were unable to do. In other words, there is no immunity against peptic ulcer in tuberculosis cases, but when a peptic ulcer occurs it does not, I think I may say with some assurance, become infected with tuberculosis when this ulcer is located this side of the pylorus. I think that this possibly has some bearing on the mucin or the protection which it affords to eroded surfaces of the mucous membrane.

Dr. Julius Friedenwald: Dr. Gray has presented a very important and interesting paper. Last year Dr. Morrison and I completed a study of the secondary gastric disturbances occurring in pulmonary tuberculosis which we, presented at the section on gastro-enterology of the Southern Medical Association. In the report we selected 100 cases of pulmonary tuberculosis of which fifty presented the initial and fifty the terminal types of dyspepsia. In the initial type the ages of the patients ranged from twenty to seventy years. Of these 76 per cent were females and 24 per cent males. In the instances of initial dyspepsia the gastric contents revealed hyperacidity in 42 per cent, normal acidity in 44 per cent and subacidity in 8 per cent and achylia in 8 per cent. The motor function of the stomach was normal in the early stages but became reduced with the progress of the affection. In the terminal dyspepsia the ages of the patients ranged from twenty-three to fifty-eight years, of which 82 per cent were female and 38 per cent male. In these cases the digestive disturbances were severe in 72 per cent, moderate in 24 per cent and mild in 4 per cent. According to our experience, as the mucous membrane becomes involved in an extensive secondary chronic gastritis the secretion of free hydrochloric acid is rapidly diminished and a true achylia is finally produced, and at the same time the motor function of the stomach becomes impaired. The gastric content at this stage reveals an absence of free hydrochloric acid and the presence of a considerable amount of mucus much in the form of swallowed clumps. In our series of cases of advanced pulmonary tuberculosis the gastric contents presented a normal acidity in 10 per cent, hyperacidity in 6 per cent, diminished acidity in 30 per cent and achylia in 54 per cent. There was, therefore, present in these cases a combined hypochlorhydria and achylia in 84 per cent. The stomach in the stage of terminal dyspepsia, therefore, ordinarily presents a high grade of motor and secretory insufficiency. These changes may occur due to the production of toxins as well as from the developing chronic gastritis. As a result there is a delayed gastric evacuation or atony. The acidity is usually reduced as well as the pepsin concentration, but the latter does not run parallel with the reduction of acidity. On the other hand, Rehfuss has pointed to the importance of visceral focal infections in resistant cases of pulmonary tuberculosis. He has been able to demonstrate in some instances infection of the bile of the gastric mucous membrane as well as of the intestinal tract with various organisms which he considers potent in causing a lessened pulmonary resistance. The secondary gastric disturbances due to pulmonary tuberculosis are, therefore, of unusual interest. This is due largely to the fact that in this disease, especially in its incipiency, the primary symptoms are frequently entirely gastric in character and consequently often overshadow the pulmonary signs. In the advanced forms, on the other hand, we are dealing with more or less severe types of chronic gastritis with marked secretory and motor changes which at this stage may result in symptoms so intense as to cause serious complications or may even overshadow those due to the primary affection.

Dr. Gray's paper is of great interest and his findings regarding the frequent presence of tubercle bacilli in the gastric contents, in the presence of lowered gastric acidity, is a valuable contribution.

Dr. Lawrason I. Brown (closing): Mr. President, tuberculous peritonitis is rare as a complication of pulmonary tuberculosis. We think that in some instances where there is a great deal of pain associated with intestinal tuberculosis that the cause of the pain may be due possibly to a localized peritonitis over the base of the ulcer. It is interesting to recall to Dr. Alvarez that when intestinal tuberculosis is most rare, pessimism is most common, i.e., in the early cases in the minimal cases. They very often start out by being exceedingly pessimistic and as the disease advances and hope is lost more and more and intestinal tuberculosis becomes more and more frequent, they become more and more optimistic.

Dr. Irving Gray (closing): We have reported this morning our findings of the studies that have been carried out for the past year.

The gastric chemistry apparently is not influenced by pulmonary tuberculosis except that there appears to be a decrease in gastric secretory power in the female group.

The intestinal complications of chronic pulmonary tuberculosis occur in many patients. There is certainly a fertile field for study relative to the prevention and treatment of tuberculous lesions of the small bowel. Undoubtedly, most of the cases of tuberculosis of the small intestine are secondary to pulmonary tuberculosis. The primary complex of tuberculosis may occasionally be found in the small bowel as pointed out by Walter Koch, of Berlin. On autopsy of the soldiers who came from South Africa, he (Koch) found after careful survey, there was no evidence of pulmonary tuberculosis in the lungs and that the primary complex with an active tuberculosis was present in the small bowel.

In the temperate zone one rarely meets with a case of intestinal tuberculosis in whom pulmonary tuberculosis is not present.

I know of a physician's wife who developed intestinal symptoms chiefly, diarrhea, with a fever between 101 and 102 degrees daily in the late afternoon. Tubercle bacilli were found in the stool and on animal inoculation, tuberculosis was established.

Studies are now being made to differentiate between the human and bovine type. Active intestinal tuberculosis will occasionally occur in humans who have no active pulmonary tuberculosis. The diagnosis depends entirely upon the findings of tubercle bacilli in the stool.

Dr. Burrill B. Crohn (closing): Dr. Ginzburg, Dr. Oppenheimer and I have been studying benign granulomata of the intestinal tract from the surgical and pathological standpoint for some time. I wish particularly to emphasize the condition which we have named terminal ileitis because that is a clinical condition to which my interest has been, for some time, directed.

Terminal ileitis presents a very definite clear-cut clinical entity. The patient presents himself apparently with symptoms of colitis. For several weeks, months, or sometimes for one or two years, one observes the complaint of diarrhea, the passage of some blood and mucus, a low grade temperature, a mild anemia. In each instance the primary diagnosis had been one of colitis. To my surprise the proctoscopic examination was regularly negative. A form of ulcerative colitis localized to the right colon or cecum suggested itself. Not only have we had experience with this localized form, but Bargen of the Mayo Clinic has described these localized areas of colitis where the transverse colon or ascending colon or splenic flexure are affected without involvement of the sigmoid or rectum. But the barium enema was again negative and we were forced to assume the existence of some lesion in the small intestinal tract to explain the condition.

In this manner we encountered a series of fourteen cases in which there existed a lesion which we did not recognize from the literature, a lesion involving eight, ten or twelve inches of the terminal ileum; a condition characterized anatomically and pathologically by tremendous thickening of the ileum, necrotizing ulcerating lesions of the mucous membrane, and the progress of this hyperplastic inflammatory condition to a stage of stenosis where the obstruction presents itself as a clinical manifestation. Sometimes the stenosing character of the lesion is apparently the first manifestation, and these cases present originally a high intestinal obstruction of a benign character. Another outstanding characteristic of this condition which we term "terminal ileitis" is the-tendency to form fistulae. Persistent abdominal fistulae are common in the experience of surgeons; medical men are not commonly called upon to analyze the formation and rationale of such persistent fistulae. Those who work in large general hospitals will find that the internists are occasionally called to the surgical side to explain why a fistula persists after an appendix operation. Terminal ileitis has similarly a great tendency to form fistulae, which tracts run usually from the terminal ileum to the cecum, sometimes to the ascending colon, very frequently to the sigmoid, sometimes through the mesentery, and sometimes to the floor of the pelvis. Sooner or later a mass appears, usually at the right side of the lower abdomen and coincident with this mass the stenotic manifestations occur. Practically all of our cases have been operated upon by Dr. A. A. Berg; the cases are today all well except one, who died at the time of operation. The other fourteen cases are well; not only are well, but they remain perfectly well after the primary lesion has been removed or sidetracked.

We have been unable to find any etiological factor which can be proved to account for this disease. We took pains to eliminate tuberculosis, syphilis, and every other recognizable agency.

One may mistakenly think that we are demonstrating a very rare lesion. Now that we are aware of the clinical condition, we are seeing at Mount Sinai at least three, four or five cases a year. We had one case two months ago, and I have now a case which will be operated upon on our return. At a session of the New York Surgical Society about four weeks ago, one of the members of that association presented a case of granuloma of the terminal ileum; to my surprise he was showing this same condition. The chairman asked for general discussion; six surgeons of large experience with abdominal conditions discussed the subject. Several men recounted having seen a case six years ago or twelve years ago, upon which he had operated with good result. These were surgeons with wide experience; several of those surgeons in the course of a lifetime had seen such lesions, but had apparently not been able to recognize or identify the underlying pathological process.

(*Slide.*) Anatomically the terminal ileum is involved for 8, 10, or 12 inches. Dr. Ginzburg mentioned 24 inches because we have such an occasional case. The terminal part of the lesion ends abruptly at this point (indicating). The depth and greatest intensity of the lesion is along the line where the mesentery is attached to the small bowel. The thickening of the wall can be seen here, the tremendous thickening of the ileum, three, four, or five times the usual thickening.

(*Slide.*) This is another specimen of the lesion, first, the normal ileum, then the beginning diseased process and the terminal part of the ileum with its maximum involvement. The stilet shows one fistula formation, here another formation. The fistula burrowed through the mesentery and made an exit at the ascending colon. In one instance while doing a sigmoidoscopy, I saw a nipple-like projection on the mucosa of the sigmoid. I was actually seeing the end of a fistula which had burrowed from the terminal ileum into the sigmoid.

(*Slide.*) This is a photograph of one of the specimens exhibited; one notes the very abrupt ending of the lesion at the ileocecal valve with the tremendous thickening at the wall of the ileum, causing what will eventually be an obstruction.

The barium enema shows a narrowing of the proximal part of the transverse colon at this point; a tentative diagnosis of a carcinoma of the transverse colon was made. However, this was a case in which a fistula had burrowed through and into the transverse colon, simulating a malignant lesion. The case was operated upon as a supposed malignancy and the benign condition was discovered at this point.

(*Slide.*) This is the last slide, demonstrating barium meal by mouth, showing the strand-like terminal ileum. At this point one sees a small fistulous tract going up to the splenic flexure.

Dr. Ginzburg (closing): I just wish to answer a few of the questions, first Dr. Bockus' question about the sigmoiditis following deep x-ray therapy. We have had no such personal experiences, but cases of that type have been reported in the literature. We know that deep x-ray therapy is very apt to cause sclerosis of the smaller vessels and I imagine the changes taking place in the sigmoid were secondary to vascular changes. Such ulcers have also been reported following deep therapy in the bladder.

As far as amebic granuloma is concerned, this report is based mainly on resected specimens and in none of them were ameba found either on section or by searching the stool. We did have a case of amebic granuloma which we thought was carcinoma of the recto-sigmoid. The removal of a specimen revealed its real nature.

As far as lues is concerned, I do not recollect any of our patients that had a positive Wassermann. I don't believe it has anything to do with the condition.

The point that Dr. Bockus brought out about the blood supply and the tendency to twist of the terminal ileum, had also entered our minds. In relation to the question of vascular changes to chronic granulomata, we said that repeated partial volvulous or intussusception may have something to do with these granulomata in the ileo-cecal region. Most of the cases as I remember them were of the slender visceroptotic type. However, we had a few patients quite the opposite, definitely stenic types.

On the question of appendicitis and terminal ileitis: At least half of the cases that finally came to operation had had their appendix removed at some earlier time. In some of those cases it was noted even at the first operation that there was something wrong with the terminal ileum. The surgeons had apparently thought, however, as they weren't quite sure what the nature of the lesion was, that they had better adopt a conservative course.

As far as tuberculosis is concerned, we have injected triturated material from the bowel wall into rabbits, guinea pigs and chickens in eight or ten instances and we have never been able to achieve any definite result. We have never been able to demonstrate tubercle bacilli in sections; never been able to demonstrate coagulation necrosis, never been able to demonstrate typical tubercles.

We have only two cases showing a definite x-ray finding with barium meal which Dr. Crohn showed. This is due mainly to the fact that a great many of these cases come in with signs of subacute obstruction and naturally one is rather loath to give them barium by mouth for fear of completing the incomplete obstruction.

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Landmark Article

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Regional Ileitis:

A Pathologic and Clinical Entity

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We propose to describe, in its pathologic and clinical details, a disease of the terminal ileum, affecting mainly young adults, characterized by a subacute or chronic necrotizing and cicatrizing inflammation. The ulceration of the mucosa is accompanied by a disproportionate connective tissue reaction of the remaining walls of the involved intestine, a process which frequently leads to stenosis of the lumen of the intestine, associated with the formation of multiple fistulas.

The disease is clinically featured by symptoms that resemble those of ulcerative colitis, namely, fever, diarrhea and emaciation, leading eventually to an obstruction of the small intestine; the constant occurrence of a mass in the right iliac fossa usually requires surgical intervention (resection). The terminal ileum is alone involved. The process begins abruptly at and involves the ileocecal valve in its maximal intensity, tapering off gradually as it ascends the ileum orally for from 8 to 12 inches (20 to 30 cm.). The familiar fistulas lead usually to segments of the colon, forming small tracts communicating with the lumen 6f the large intestine; occasionally the abdominal wall, anteriorly, is the site of one or more of these fistulous tracts.

The etiology of the process is unknown; it belongs in none of the categories of recognized granulomatous or accepted inflammatory groups. The course is relatively benign, all the patients who survive operation being alive and well.

Such, in essence, is the definition of a disease, the description of which is based on the study, to date, of fourteen cases. These cases have been carefully observed and studied in their clinical course; the pathologic details have resulted from a close inspection of resected specimens from thirteen of fourteen patients operated on by Dr. A. A. Berg.

Relationship of Regional Ileitis to Other Benign Intestinal Processes

There exists in the medical literature a heterogenous group of benign intestinal lesions which have now and then been described under the caption of "benign granulomas." The latter loose term covers a multiplicity of conditions in which both large and small intestines may be involved; it includes all chronic inflammatory lesions of the intestine whose etiology is either unknown or attributable to an unusual physical agent. It represents a hodge-podge or melting-pot in which are thrown all those benign inflammatory intestinal tumors which are neither neoplastic nor due to a specific bacterial agent. Within this group one finds descriptions of foreign body tumors, chronic perforating lesions with gross inflammatory reactions, traumas of the mesentery with intestinal reactions, Hodgkin's granuloma, a late productive reaction to released strangulated hernias of the intestinal wall and numerous other and similar conditions. The so-called benign granulomas all present a tumor-like inflammatory mass which usually simulates carcinoma but which eventually unmasks itself as probably an infectious process of unknown causation. The multiplicity of the possible sites of gastric, intestinal or colonic involvement and the accompanying protean clinical manifestations defeat any effort to include them all in a clear cut clinical entity. The very confusion defies classification.

In this literature, however, there have appeared on occasions references and descriptions that approach the picture that we are about to describe. The entire literature of benign granulomas was reviewed in 1920 by Tietze (1), who not only described his own cases but covered all previous medical publications. There is nowhere in his encyclopedic article a description which resembles that of regional ileitis. In 1923, Moschcowitz and Wilensky (2), in describing four cases of benign intestinal granuloma, detailed one case of a disease involving the terminal ileum which closely resembled that in our cases. They grouped it with various other and similar colonic masses as granuloma. Mock (3) in 1931 again described granuloma, but included no example that resembled the cases we have studied.

Just as the generic term of typhus originally included various diseases, from which group eventually typhoid fever, Brill's disease, Rocky Mountain fever, tabardillo and others were split off, so, similarly, do we aim to disintegrate from the general group of varied diseases spoken of as a "benign granuloma" a specific clinical entity with constant and well defined characteristics, which we propose to name "regional ileitis."

Pathologic Anatomy of the Disease

All the specimens obtained by resection were in patients who had been ill for at least a year. We therefore have no specimen exhibiting the very early phases of the disease. The latter are sometimes encountered at the operating table following an illness of from one to two weeks and diagnosed, as a rule, as acute appendicitis. At this time the terminal ileum is found thickened, soggy and edematous; the serosa is a blotchy

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red. The mesentery of the terminal ileum is greatly thickened and contains numerous hyperplastic glands. Owing to the possibility of spontaneous resolution, resection has never been performed at this stage, so that we have no knowledge of the intra-intestinal changes present at this time.

The inflammatory process is not, however, a static one, nor is the entire diseased segment affected at one time. The oldest lesions begin apparently at, or just oral to, the ileocecal valve, and the more recent ones are situated proximally. In some of our relatively early cases, we have found isolated lesions separated from the main hypertrophic mass by normal mucosa. These isolated areas are, in our opinion, the earlier and primary lesions of the disease; they consist of oval mucosal ulcerations, about 1 cm. in diameter, located on the mesenteric border of the small bowel and lying in the long axis of the intestine, where a sort of groove is naturally formed by the attachment of the mesentery.

The characteristic, fully developed hypertrophic process is, as a rule, limited to the distal 25 to 35 cm. (10 to 14 inches) of the terminal ileum, including the ileal side of Bauhin's valve and terminating rather abruptly at that point. The most advanced pathologic changes are present at the valve, which in some instances becomes converted into a rigid diaphragm with a small irregular opening. Proximally the severity of the process gradually abates, shading off into normal mucosa. The normal intestinal folds are distorted and broken up by the destructive ulcerative process and rounded and blunted by edema, giving a bullous structure to the mucosal aspect of the intestine, or frequently a cobblestone appearance of the surface of the mucosa may result. A series of small linear ulcerations lying in a groove on the mesenteric side of the bowel is almost always present. Whether these are the remnants of the original ulcerative lesions or whether they are mechanical erosions due to the formation of a *darmstrasse* by the shortening of the fibrotic mesentery, it is impossible to say.

The submucosal and, to a much lesser extent, the muscular layers of the bowel are the seat of marked inflammatory hyperplastic and exudative changes. As a result of these, the wall of the bowel becomes enormously thickened, frequently reaching two or three times its normal density. The lumen of the bowel is greatly encroached on, becomes irregularly distorted and, at times, is only large enough to admit a medium-sized probe. The intestine proximal to the involved segment frequently, but not invariably, becomes greatly dilated and may show superficial irregularly placed tension ulcers. When seen at the operating table, the involved loop is a soggy hoselike mass.

In the older phases of the disease, the exudative unusual reaction is replaced by a fibrostenotic process, and the mucosa appears atrophic with occasional superficial erosions and islands of papillary or polypoid hyperplasia. The serosa loses its gloss and frequently exhibits tubercle-like structures on its surface. The mesentery of the affected segment is greatly thickened and fibrotic, as is the subserosal intestinal fat.

A marked feature is the tendency toward perforation. Free perforation into the peritoneal cavity has not been encountered in this series. The chronic perforation apparently occurs slowly enough to permit of walling off by adhesions to a neighboring viscus, to the parietal peritoneum or to the omentum. There is a marked tendency to the formation of internal fistulas, the sigmoid having been the seat of fistulous involvement four times and the ascending colon and cecum once each. The walled-off abscesses resulting from slow perforation into the peritoneal cavity are, as a rule, considered appendicular in origin. When drained, they give rise to chronic intractable fecal fistulas which defy attempts at simple closure because of the persistence of the underlying inflammatory disease in the bowel. Indirect perforation of the cecum may result from perforation of the ileum into the terminal mesentery with secondary cecal termination of the fistulous tract. Pericecal fibrotic and inflammatory changes which result from the proximity of the ileal focus to the cecum are probably responsible for the roentgenologic changes in the contour of the ascending colon and cecum, such as may be easily confounded with the defect of hyperplastic tuberculosis.

Microscopically, no specific features can be demonstrated. The stained histologic sections showed various degrees of acute, subacute and chronic inflammation, with variations in the predominance of polymorphonuclear, round cell, plasma cell and fibroblastic elements. In the early stages the lesion is a diffuse one, involving mainly the mucosa and submucosa, with the presence of some inflammatory serosal reaction. The mucous membrane shows areas of marked destruction, and at times the glandular structure is almost completely gone, leaving an atrophic layer of epithelium, the result of a regenerative process. In later stages of the disease, the inflammatory reaction is more focal in character. These focal areas of inflammation in the serosa give the appearance, on gross examination, of tubercles.

In some of the cases, the presence of giant cells is quite striking. Special stains have occasionally demonstrated the presence of large pale cells, or groups of cells, probably vegetable in nature, in the vicinity of the giant cells. They could be demonstrated frequently in all the layers of the intestine. These and the giant cells are probably not an essential feature of the pathologic changes in this condition. They are, more likely, accidental findings due to the inclusion of small particles of vegetable matter which have become entrapped in the ulcers, entered the lymphatics and become encapsulated in the process of healing. The resultant foreign body reaction around these nonabsorbable particles results in the presence of the giant cells. To some extent they may be contributory to the marked hypertrophic scarring which occurs. We believe that the attempts, by some authors, to classify this granulomatous condition as an exudative unusual form of tuberculosis were, to a great extent, predicated on the assumption that the giant cells were, necessarily, evidences of tuberculosis.

It is quite likely that in the past this granulomatous condition was confounded with ileocecal tuberculosis, and so missed as a clinical and pathologic entity. The failure of the pathologic reports in our cases to substantiate a suspicion of tuberculosis led us to exercise still greater caution in eliminating a Koch infection as the etiologic agent. With the assistance of Dr. Paul Klemperer in determining moot points, sections from the various cases were again reviewed. No evidences of tuberculosis, syphilis, actinomycosis, Hodgkin's disease or lymphosarcoma were found. Guinea-pig, rabbit and chicken inoculations of triturated material from mesenteric glands and from the intestinal wall proved negative for tuberculosis in five cases. Löwenstein tubercle cultures were also negative in three instances. It is interesting to note that none of these clinical cases presented any evidence of pulmonary tuberculosis; there were no positive Wassermann reactions in this series.

The relation of appendicitis and previous operations to the development of the disease is of some interest. Half the patients had been subjected to appendectomy before the final resection was performed. In about half of those cases, abnormalities of the terminal ileum were already noted at the time of that operation. In those cases in which there had been no previous appendectomy, the mucosa of the appendix was not involved, as might be expected from the fact that the disease stops on the ileal side of the valve. Inflammation of the outer coats of the appendix, due to the presence of adjacent inflammatory disease, was common.

The Clinical Features

Etiologically, young adults comprise the largest number of patients. Only two of the patients studied were over 40 years, the average incidence being at 32 years of age; the youngest patient was 17, the oldest 52. Males predominate over females in the proportion of nearly 2:1. There are no known predisposing factors.

Cases of regional ileitis run, in general, a fairly constant and typical clinical course. Most of the patients had been ill for from several months to two years before coming under observation. During this time the outstanding complaints were fever, diarrhea, continuous loss of weight and a progressive anemia. The clinical picture resembles that of a nonspecific ulcerative colitis.

Fever is rarely high, long periods of apyrexia being interspersed with shorter and irregular cycles of moderate temperature. Occasionally, though rarely, the temperature rises above 103°F. Some of the cases run the complete course without fever.

Diarrhea is usually an outstanding feature, though the number of movements and the intensity of the actions never approach those of a true colitis. The average patient has from two to four loose or semisolid daily defecations, sometimes with blood and always with mucus. The stools are rarely mushy or liquid and contain free pus, coagulated lumps of mucus and streaks of blood, but tenesmus is always lacking. There are none of the perianal fistulas, condylomas or perirectal abscesses that characterize the complications of true colitis, for in this disease the rectum and colon are never involved. At times, particularly when the stenotic factor predominates, as in the later periods of the course, constipation rather than diarrhea predominates.

Vomiting characterizes the stenotic type of cases, is never marked or persistent and is usually accompanied by abdominal pain and visible peristalsis.

Pain distributed over the lower abdominal parietes is a common feature of the disease. This pain is dull and cramplike and accompanies, or is followed and relieved by, defecation. It is usually localized to the right lower quadrant and is occasionally referred across the abdomen to the whole lower abdominal region. Occasionally, and not infrequently, when the sigmoid, as is not unusual, becomes adherent to the necrotizing hyperplastic ileum, fistula formation occurs between these two hollow viscera. In these cases the pain is mainly localized over the left lower abdominal quadrants; the mass which is then felt abdominally and per rectum may appear to be an integral disease of the rectosigmoid area.

The general symptoms are those of weakness, usually a rapid and progressive loss of weight, and an anemia which ordinarily is moderate, but which may progress to a severe degree. In the milder cases, however, there may be little or no emaciation and no anemia. The stools contain constantly occult blood. Appetite is poor, particularly during the febrile bouts.

A moderate leukocytosis characterizes some of the cases; in most, the white blood count is normal. Even in the stenotic cases the blood plasm findings that accompany marked obstructions of the upper alimentary tract are rarely seen.

Physical Examination

Certain physical findings characterize this disease, the most constant ones being (1) a mass in the right iliac region, (2) evidences of fistula formation, (3) emaciation and anemia, (4) the scar of a previous appendectomy and (5) evidences of intestinal obstruction.

1. A moderate-sized mass is usually felt in the lower right iliac region or in the lower midabdomen. The mass is usually the size of a small orange, tender, firm, irregular and only slightly movable. This mass is composed of the tremendously hyperplastic ileum, the stenotic inflamed ileocecal junction, which may and often does assume a size of from two to five times that of a normal valve of Bauhin, and frequently an adherent section of the colon or sigmoid to which a fistulous tract has been created. When the sigmoid is adherent and involved, the mass may lie more to the left; when the cecum or ascending colon or hepatic flexure constitutes the distal end of the fistulous tract, the mass may lie more to the right and higher in the abdomen. When the fistulous tract burrows into and through the mesentery, the necrotic process may cause a diffuse mesenteric suppuration which participates in the formation of the mass. The tumor is usually palpable per rectum, though felt only very high with the examining finger.

2. Fistula formation is a constant feature of the disease process. The most common site of adherence is the sigmoid; next in frequency is the cecum and the ascending colon and occasionally the hepatic flexure. As the necrotizing process of the mucosa of the ileum progresses through its several coats, the serosa becomes involved. Any hollow viscus, usually the colon, now becomes adherent to the point of threatened perforation. A slowly progressive perforation is thus walled off, but results in a fistulous tract being formed between the two viscera. In one case the uterus formed the limiting organ of a threatened perforation. In another case, on sigmoidoscopic examination, a nipple-like papillomatous projection was seen high in the rectum, or just above the rectosigmoid angle. This observation was noted at the time, but the proper interpretation was overlooked; it was the colonic end of a perforating fistulous tract. In still another case, the anterior abdominal wall presented a fecal fistula, particularly such as persists after a fruitless appendectomy. These fistulas are usually regarded as cecal in point of origin; they are always, however, communications between the necrotic ileum and the anterior abdominal wall.

3. There are evidences of emaciation and anemia.

4. In at least half of the cases the appendix had been removed at some previous operation. This appendectomy usually antedated by several months or years the present symptoms. In many cases the appendix had been removed several months previous, at which time thickening and tumor-like massive inflammation of the small intestine and mesentery had been noted, though nothing beyond the appendectomy had been attempted. It seemed quite evident that in these cases the lower right abdominal symptoms had resulted in the discovery or in the overlooking of the real pathologic process in the terminal ileum. In all such cases the pathologic report cited "acute and chronic inflammatory changes of the appendix," a report which really whitewashed this organ as a participant in the disease process. In fact, we now know that the process never transcends the limit of Bauhin's valve, and that the appendix is always free from guilt and free from changes.

5. In those cases in which the process has progressed to a stenotic stage, the physical findings are those of intestinal obstruction. Loops of distended intestine may be visible through the emaciated abdominal wall, and puddling is frequently observed in the flat x-ray plates. Visible peristalsis is not uncommon and is accompanied by borborygmus and the passage of gas with evident relief. The visible loops of the distended intestine are usually localized to

the lower midabdomen. General distention and ballooning of the whole abdomen are unusual.

Clinical Course of the Disease

There are four various types of clinical course under which most of the cases may be grouped: (1) acute intra-abdominal disease with peritoneal irritation, (2) symptoms of ulcerative enteritis, (3) symptoms of chronic obstruction of the small intestine, and (4) persistent and intractable fistulas in the right lower quadrant following previous drainage for ulcer or abdominal abscess.

1. *Signs of Acute Intra-Abdominal Inflammation.* — It is impossible to distinguish these cases preoperatively from those of acute appendictis. There are generalized colic, pain and tenderness in the right lower quadrant and fever up to 101° or 102°F. The white blood count is elevated. The development of symptoms seems to be somewhat slower than in appendicitis. The presence of a mass even without actual abscess formation is a fairly constant feature. The picture encountered at operation is that of a greatly thickened, red or blotchy terminal ileum, with marked edema of the surrounding tissues and slight exudate of the ileal wall. The mesentery is thickened and edematous, and contains numerous large glands. There is usually clear fluid present in the abdomen. The appendix may appear, and shows evidence of a periappendicitis without mucosal involvement. In some cases an abscess is encountered; in our experience the pus has been thick and grumous, and not as foul smelling as an abscess of appendiceal origin. The future course of these cases cannot be predicted. Some seem to undergo resolution, others to pass into one of the more chronic phases of the disease. Those cases which are drained may develop intractable fistulas.

2. *Symptoms of Ulcerative Enteritis.* — These patients complain of colicky periumbilical or lower abdominal pain. There is a tendency toward looseness of the bowels (from three to five movements a day). The stool is usually liquid or mushy and contains pus, mucus and occult or visible blood. There is no gross melena. A constant fever is present, but the temperature is rarely above 100°F.

With the progress of the disease, a marked secondary anemia may develop, reaching as low as 35 per cent hemoglobin. Considerable loss of weight and strength may occur. In some instances disturbances of general nutrition are slight. This course may continue for as long as a year until exhaustion sets in, or more commonly the cases pass gradually into the stenotic phase of the disease.

3. *Stenotic Phase.* — This is the type most commonly encountered. The symptoms in this stage are those of a subacute or small intestinal obstruction of varying severity. The obstruction, as in most obturating lesions of the small bowel, is not complete. Violent cramps, borborygmus, occasional attacks of vomiting and constipation are present. Visible peristalsis and intestinal erection are common. A palpable mass is practically always present in the lower right quadrant. In this phase of the disease fistulous communications with the colon or sigmoid may lead to the signs and symptoms of colitis, and mask the true nature of the disease. Occasionally the stenotic phase occurs as a primary manifestation of the disease; again, the symptoms may have been present for years (four years in one of our cases).

4. *Persistent Fistulas.* — Even before we had had a resected specimen to confirm our suspicion, we felt that a certain number of the persistent and intractable intestinal fistulas which followed on the drainage of a supposedly appendiceal abscess were in reality due to a nonspecific inflammatory disease involving the terminal ileum. This belief was founded on the following observations:

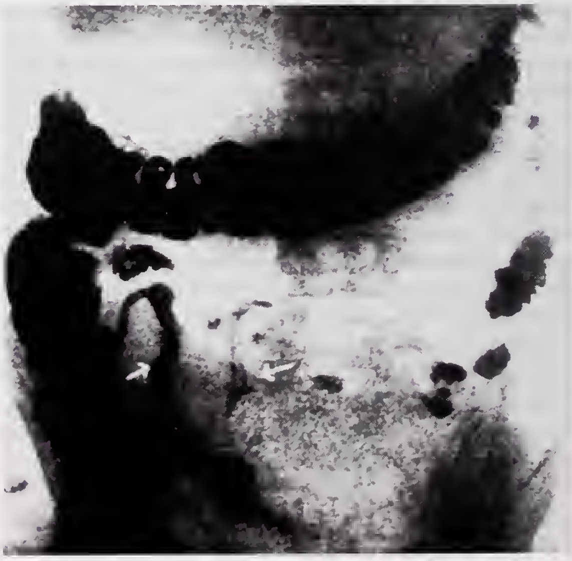
1. In a number of instances at the time of the second or third operation for closure of the fistulas, the appendix was found intact and not diseased.
2. Removal of the specimens from the sinus tract and from the intestinal end of the fistula failed to reveal any evidence of tuberculosis or other specific disease.
3. The occurrence of ileal without cecal origin of the sinus tract was noted.
4. The tendency of fecal fistulas of simple appendiceal origin is to close spontaneously or to be susceptible of closure by excision of the tract and inversion of the stump.

However, in two instances resection of the intestine and fistulous tract revealed the typical pathologic picture of ileitis. We assume, therefore, that fistulas which are of supposedly appendiceal origin, but which have ideal openings and which have resisted simple surgical closure are, in the absence of tuberculosis, to be considered as cases of regional ileitis. One peculiar feature of these fistulas may be remarked: They may develop a few months after the original drainage operation, the wound meanwhile having healed and having remained healed for a few months. An abscess then develops in the wound; when this abscess mass is investigated, a communication with the intestine may be demonstrated.

Roentgenographic Observations

Two outstanding facts, one negative and the other positive, are regularly noted. Since the disease simulates regularly the clinical characteristics of ulcerative colitis, the barium enema is first attempted. This procedure results in a negative report. The reason for this is evident in the light of the pathology of the disease. The colon is uniformly free from changes, even though the ileocecal valve is the seat of greatest intensity of the process.

The barium meal, however, when carefully interpreted, gives definite positive findings. These usually consist of distended loops of terminal ileum, in which a fluid level is discernible, and a definite delay in motility of the meal through



Roentgenogram of the barium meal given by mouth, showing regional ileitis. Note the extent of the strictured area.

the distal end of the small intestine. In the four, six and nine hour observations this delayed motility is usually present, though only in the late or stenotic stages is the delay striking. The milder degrees of stasis and puddling in the deal loops may easily be overlooked by any but a careful roentgenologist. Even when the condition is plainly indicated, the true significance of these reported results may be glossed over by the clinician and an exact diagnosis may thus be missed.

When the ascending colon is the seat of a fistulous communication with the ileum, one may note some stricture deformity of the ascending colon or hepatic flexure, with delayed motility at this point. When the sigmoid is similarly involved in a fistulous tract, a true narrowing and delay at this flexure may simulate carcinoma and so create the necessary indication for operation. Both these areas of stenotic deformity of the large bowel are incidental to only one of the complications of the disease, namely, the formation of fistulous tracts. The entire colon is otherwise exonerated as a primary site of the granulomatous inflammation.

Differential Diagnosis

Regional ileitis must be differentiated from several analogous conditions which produce a mass in the right iliac region with diarrhea and fever. The most important differentiation is that of regional ileitis from nonspecific ulcerative colitis. The sigmoidoscopy and the barium enema suffice for the recognition of colitis in the largest percentage of cases. But there are types of colitis which involve only the proximal segments of the colon, and in which the sigmoid and the rectum are free from pathologic: changes. While these instances are few and relatively uncommon, they do occur and lead to much confusion; they may be recognized by the deformity and spasm of the cecum and ascending colon when the latter areas are the seat of the segmental phenomena of colitis. Only in severe cases of ulcerative colitis does the process involve the terminal ileum, and then only for a few inches. In regional ileitis, all of the damaged tissue is proximal to the valve. The diagnosis is purely roentgenographic, the clinical differentiation being impossible. Colitis does not cause fistulas except about the anus and rectum; a mass is rarely palpable in colitis.

Ileocecal tuberculosis as a primary process should be easy of differentiation from regional ileitis. We are inclined, however, to agree with Moschcowitz and Wilensky (2) in the skepticism with which they view the actual occurrence of a primary tuberculous process at the ileocecal junction. To repeat their arguments, the latter disease must be rare, for only three cases have been seen at Mount Sinai Hospital in several years. Pathologic examination of all such suspected tuberculous masses has uniformly failed in the demonstration of tubercles or of tubercle bacilli in the sections or smears. Practically all cases mistakenly suspected of, or diagnosed as, ileocecal tuberculosis have been eventually classed as new growth, as appendicitis with abscess or as benign nonspecific granuloma. In all of our first cases of regional ileitis the diagnosis of ileocecal tuberculosis was the unvarying best possibility; operation was undertaken only after the customarily accepted methods of treatment for tuberculosis had been exhausted. Fibroplastic appendicitis or typhlitis is a disease better known to the surgeons.

Lymphosarcoma, intestinal or mesenteric tuberculosis and Hodgkin's disease simulate regional ileitis in many of its features. The exact differentiation is possible only at the operating table or by the examination of pathologic specimens. Sarcoma of the intestine is usually multiple, causing dilatations at various levels, and involves the jejunum as well as the ileum and not particularly just the terminal 8 to 12 inches of the small intestine. Hodgkin's disease may give its characteristic monocytic blood picture, or a regional lymph node may reveal the true nature of the process.

Actinomycosis of the ileocecal region with fistula formation to the external abdominal wall must always be mentioned in the differentiation from ileitis. The extreme rarity of actinomycosis in this region of the body and in this climate makes this differentiation more theoretical than necessary.

From carcinoma of the terminal ileum or of the ileocecal valve the differentiation cannot be made with any certainty; both conditions call for surgical intervention and both lead to cure by successful and early resections.

Treatment

Medical treatment is purely palliative and supportive. The diseased area cannot be reached by colonic irrigations or enemas, and any attempts by medical means to reach a necrotizing, ulcerating and stenosing inflammation of the terminal ileum is purely and essentially futile. True, one case, discovered in the course of a cholecystectomy for stones, progressed to spontaneous healing or at least to a cessation of the intestinal symptoms.

But in general, the proper approach to a complete cure is by surgical resection of the diseased segment of the small intestine and of the ileocecal valve with its contiguous cecum. The restitution to complete health in thirteen out of fourteen cases as a result of the radical resection of the pathologic process or of a short-circuiting operation speaks vehemently in favor of surgical methods as the logical successful therapeutic procedure.

In one instance recurrent symptoms were accounted for by the finding of an annular stenosis a short distance proximal to the new anastomosis (ileotransversostomy). Apparently in this case the resection had not been carried out sufficiently oral to the lesion completely to eradicate the disease.

Our experience with short-circuiting anastomoses is limited. In one case a short-circuit ileocolostomy was performed through a segment of ileum that was apparently normal at the time of operation. The pathologic process did not heal; on the contrary, the disease progressed to the proximal loop of the anastomosis. In two cases of intractable fistulas and in one case of inflammatory pelvic mass, ileocolostomy with exclusion has given excellent results. The best operation, as devised by Dr. A. A. Berg, consists of dividing the ileum 3 feet (91 cm.) from the ileocecal junction, closing both ends of the divided ileum and implanting the proximal terminus of the ileum by a side-to-side anastomosis at the transverse colon.

Abstract of Discussion

Dr. J. A. Bargen, Rochester, Minn.: This presentation would seem timely, for, with improved roentgen technic and more intensive study of intestinal disease, the condition may prove to be less common than it is now supposed to be. Intensive roentgenologic investigation often becomes necessary to determine the nature of disturbances of the ileocecal coil. Undoubtedly some of these cases have been overlooked. In the last few years, several cases annually of this type have come to operation at the Mayo Clinic. Usually the appendix has been removed for complaints similar to those for which the patients presented themselves, that is, recurrent and intermittent attacks of right abdominal pain and discomfort. Some of these conditions were diagnosed preoperatively because of the suggestive roentgenographic and roentgenoscopic signs. The lumen of the intestine in this region is narrowed, and the wall is thickened and shortened. The gross appearance of the removed specimen resembles closely that of the colon in advanced chronic ulcerative colitis. The lesion is inflammatory, containing fibrotic elements and granulation tissue as well as evidence of more acute changes. The evidence points to a regional inflammatory disease perhaps on the basis of localized decrease in resistance to some bacterial invasion. I am wondering whether the designation "terminal" is adequately descriptive. To some it has conveyed the meaning of agonal. Perhaps the modifying adjective "regional" or some other word suggesting its localized nature, instead of the end, would be more suitable: I should like to emphasize that this presentation is an important one, that possibly these cases will be discovered earlier and more frequently in the future, and if so, one instead of two operations may be performed, and that I believe the lesion is infectious.

Dr. Julius Friedenwald, Baltimore: I am reminded of two cases quite a number of years back in which this condition was evidently present but which were regarded at the time as instances of carcinoma. Both patients, men, presented almost identical symptoms; the one was 50 and the other 58 years of age. The condition arose in the midst of good health and was associated with rapid loss of flesh, diarrhea, indigestion, slight fever and anemia; it terminated in progressive constipation and in attacks of partial and almost complete obstruction. In both instances an indefinite mass could be detected in the cecal region. At operation an extensive obstructive mass was detected in the terminal ileum. A diagnosis of inoperable carcinoma was made by the surgeon and a lateral anastomosis performed. The patients made a surprisingly rapid recovery and remained well. The recovery could not be explained at the time, but the condition was evidently ileitis, as described by the authors. Since then I have observed a number of instances of a milder type which at operation presented a somewhat similar appearance. In a woman, aged 62, who was operated on about two years ago and who presented symptoms of lower right-sided abdominal pain with loss of flesh and attacks of alternating diarrhea followed by intense constipation, this condition was observed in the terminal ileum in a mild form. The surgeon, not realizing its significance, simply removed a chronically inflamed appendix. Since then the attacks have continued, the distress becoming more marked. The authors have undoubtedly described a clinical entity of great importance, a condition that may occur in so severe a form as to simulate carcinoma or intestinal tuberculosis or, in a milder form, presenting the appearance rather of a chronic appendicitis. The possibility of its occurrence must constantly be borne in mind in the differential diagnosis of chronic abdominal disease.

Dr. Louis J. Hirschman, Detroit: I have just such a case under my observation, which presents an interesting phase which has not come under the observation of the authors, at least but rarely, as I recall their paper. This is a youth, aged 18 years, who has been suffering from chronic ulcerative colitis since 9 years of age, half his life. His weight has gone down in the last few months to 78 pounds (35.4 kg), so much so that when he was sent to me for surgical relief for his chronic ulcerative colitis, having hemorrhages, I decided on intestinal rest and enterostomy was performed. A diagnosis of benign papilloma of the ileum was not made. He was sent for relief from the chronic ulcerative colitis. At operation, about 12 inches (30 cm) of a large, doughy, thickened ileum was discovered. It was resected and ileostomy done, with immediate relief. The appendix also was involved. It was done about eight weeks ago and the patient has gained weight so that he weighs now about 130 pounds (59 kg). The interesting point to me is that when the specimen was opened the ileum was almost occluded with granulomas. It was a wonder he had any peristalsis or intestinal movement. I gathered from what the authors said that it is uncommon to have an ulcerative colitis in connection with a granulomatous infection of the terminal ileum. In this case there was no evidence of fistulas in connection with either the terminal ileum or the large intestine and I wondered why, since there is the granulomatous formation they described.

Dr. Sidney A. Portis, Chicago: What were the bacterioscopic observations on the excised portion of the ileum? Did you make any sections of the ileum to find out whether any bacteria were deeply seated in the walls of the ileum?

Dr. Burrill B. Crohn, New York: In a disease of this type, in which an attempt is being made to establish the etiology of the disease, we have naturally taken great pains to exclude every known etiologic factor. Histologic sections were made of the tissues and stained with various types of stains. Cultures were made. Ground material was injected into guinea-pigs and fowl. Various types of laboratory animals were used to eliminate any possible form of tuberculosis. Löwenstein cultures were made. Dr. Klemperer, the pathologist, exhausted all the known possible scientific methods of finding an etiologic factor. I can say that no etiologic factor was found. It is refreshing to address a medical organization of this kind, where one can count on meeting men of large clinical experience and find that Drs. Bargen, Friedenwald and Hirschman have seen cases of this type. I have not had many occasions, in fact this is the first, to read this article. I have spoken extemporaneously at one or two previous meetings and wherever I spoke of this subject, the older clinicians, men with broad experience, surgical or medical, always have said: "We have seen such a thing in past years. We have met with it in surgical experience and didn't know what to do with it." The chairman of the New York Surgical Society, at the time the subject was brought up, said: "I have to operate in such a case and I don't know what to do. I don't know the nature of it." I forgot to mention an important physical sign; namely, the mass that occurs. In these cases a mass develops in the lower abdomen, usually in the right ileac region, consisting of agglutinated coils of ileum massed together. Sometimes the mass will move over from adhesions to the sigmoid and will present more in the left lower abdomen. The mass can usually he felt by rectum. It is a hard mass and a movable mass. it does not feel carcinomatous, though I must say some of the best cases we met had previously been condemned as inoperable carcinomas. In addition to the agglutinated loops of ileum, an inflammatory reaction is set up by the fistulas that travel through the mesentery of the ileum to the loops of the colon. I am thankful for the discussion. I had come to the conclusion that only the abdominal surgeons knew about the condition. I am glad to find that men with older and larger medical experiences have also met with the manifestations of the disease.

Dr. Frank Smithies, Chicago: You never found free fluid, did you?

Dr. Crohn: Yes, a small amount, not demonstrable by physical signs but a small amount such as one would find in any inflammatory peritoneal lesion — real ascites.

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ANNOUNCEMENT OF 1999 AWARDS

The Mount Sinai Journal of Medicine offers several prizes for manuscripts published in *The Journal* during the previous year and judged by an awards committee to be outstanding contributions to the medical literature. The committee's task certainly was formidable, but I believe that it has chosen wisely and well. The efforts of the members are much appreciated.

The 1999 Joseph Globus Award, established in honor of the first and long-time editor of *The Journal*, is for the best overall paper on a clinical topic. The award goes to Harold C. Sox, M.D., for his paper "Current Controversies in Screening: Cholesterol, Breast Cancer, and Prostate Cancer," Volume 66, No. 2, pp. 91–101.

The 1999 Ralph Colp Award, in honor of the memory of a distinguished chief of surgery at The Mount Sinai Hospital, for the best paper on a surgical topic, goes to Nelson N. Stone, M.D. and Richard G. Stock, M.D., for their paper "Laparoscopic Pelvic Lymph Node Dissection in the Staging of Prostate Cancer," Volume 66, No. 1, pp. 26–30.

The 1999 Student Award, for the best paper submitted by a medical student, goes to Nina Desai, for her paper "Intussusception in Adults," with Michael G. Wayne, M.D., Peter J. Taub, M.D., Marc A. Levitt, M.D., Renee Spiegel, M.D., and Unsup Kim, M.D., Volume 66, No. 5, pp. 336–340.

On behalf of the Editorial Staff, I am delighted to recognize the outstanding scholarship and contributions of our 1999 awardees to medicine in general, and to *The Mount Sinai Journal of Medicine* in particular.

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THEME ISSUE
MINIMALLY INVASIVE TECHNIQUES IN NEUROSURGERY

Martin H. Savitz, guest editor

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Introduction

The Advent of Minimalism in Neurosurgery

Martin H. Savitz, M.D.

Neurosurgical minimalism, the concept of operating on the nervous system through the least damaging route and by the most precise instrumentation, originated early in the 20th century.

Harvey Cushing, the father of American neurosurgery, was still in training at The Johns Hopkins Clinic when the first successful transsphenoidal approach to removing a pituitary tumor was performed by Schloffer (1) in 1907. Endoscopy and minimally invasive surgery of the brain date back to 1910, when Lespinasse (2) introduced a small cystoscope into the ventricles of two hydrocephalic infants in an attempt to fulgurate the choroid plexus. In 1937, Pool (3) illuminated a simple cannula with a modified otoscope to perform myeloscopic examination of the cauda equina; direct visualization of the dorsal nerve roots allowed the differential diagnosis of herniated nucleus pulposus, hypertrophied ligamentum flavum, adhesive arachnoiditis, benign neoplasm, and metastatic carcinoma. As early as 1939, Love (4) advanced the basic principle of microdiscectomy, interlaminar removal of a protruding intervertebral disc with a small incision and without resection of bone. Stereotactic surgery — directing the tip of a needle in three planes to a predetermined locus inside the skull — was based on the pioneering work of Spiegel et al. (5) in 1947 and Leksell (6) in 1949.

Neuroradiology began in 1918, when Dandy (7) intentionally replaced ventricular fluid by air to obtain radiographs of the cerebral ventricles. The use of Lipiodol to outline the spinal subarachnoid space was devised by Sicard and Forestier (8) in 1922 as an aid in the localization of spinal cord tumors. Moniz (9), in 1934, was the first to perform carotid angiography, in an attempt to opacify the intrinsic vessels of the brain. By the end of World War II, the increasing availability of pneumoencephalograhy, myelography and cerebral arteriography made it possible to provide correlative roentgen diagnosis and localization in diseases of the nervous system. Refinement continued with stereoscopic views, magnification and subtraction technique. Noninvasive imaging was finally possible when Hounsfield (10) introduced computerized transverse axial scanning in 1973.

Minimalism in neurosurgery became centered on microsurgical technique in 1955, when Malis (11, 12) employed a binocular microscope to operate on an animal brain, along with bipolar coagulation, which provided limited cautery between the ends of a microforceps and kept the intrinsic cerebral arteries patent. Kriss and Kriss reported that Kurze, in 1957, was the first neurosurgeon to bring a microscope into the operating room to assist in removing a neurilemoma of the seventh cranial nerve (13). The concepts of microneurosurgical technique included establishing the diagnosis by neuroradiological studies, planning the smallest approach, and avoiding exploration, to minimize tissue dissection. Williams (14) had unique motivation to employ microlumbar discectomy, namely treatment for Las Vegas showgirls, who could not display more than a one-inch incision or stay out of work more than two weeks.

Research into minimally invasive disc surgery with chymopapain was reported in 1963 by Smith et al. (15). Percutaneous discectomy started with the work of Hijikata (16) in 1977. Arthroscopic microdiscectomy was developed by Kambin (17) in 1983, and Ascher (18) was the first to utilize a neodymium: yttrium-aluminum-garnet laser to ablate the nucleus pulposus through an 18-gauge spinal needle.

Key Words: Minimalism, neurosurgery

Following the adaptation of nuclear magnetic resonance for viewing the anatomy of the nervous system, the advances in neuroimaging became exponential, including magnetic resonance angiography and 3-dimensional computerized tomography. Today, frameless stereotaxy, sonic digitizers, robotic instrumentation, real-time imaging, and the interfacing of digital and video imaging are becoming part of every neurosurgical training program. Alternating between direct observation of surface features and indirect visualization of deep structures with high-resolution, high-definition systems will further the neurosurgeon's ability to accomplish minimally invasive surgery of the brain and spine.

Yet it would be misleading to focus entirely on noninvasive neuroimaging, miniaturization of instrumentation, and improved intraoperative viewing of lesions. Endovascular stenting and coiling of aneurysms and arteriovenous malformations, stereotactic radiosurgery, implantation of electrodes, simple shunting methods, nonoperative pain management, chemonucleolysis and computerized-tomography-guided needle procedures also further the objectives of minimalism. In the immediate future, gene therapy for cerebrovascular disease and viral treatment of brain tumors may become new standards of minimally invasive techniques in neurology and neurosurgery.

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Lumboperitoneal Shunts

Haq Babur, M.D.[1], Quirico Torres, M.D.[2], and Martin H. Savitz, M.D.[3]

Abstract

Background: To assess lumboperitoneal shunting as a simple method of relieving communicating hydrocephalus, treating pseudotumor cerebri, and resolving cerebrospinal fluid fistulae.
Method: Three neurosurgeons at different hospitals report their combined experience over a 20-year period.
Results: Ease of insertion of the device and low rate of complications were reported in a combined series of 107 patients.
Conclusions: Lumboperitoneal shunting is a technically simple and highly effective surgical technique for diversion of cerebrospinal fluid. **Key Words:** Lumboperitoneal shunts, communicating hydrocephalus, cerebrospinal fluid fistula, pseudotumor cerebri.

In 1975, Spetzler and co-workers (1) introduced a new silastic lumboperitoneal shunt which could be introduced percutaneously without the need for formal laminectomy or laparotomy. While the shunt's primary intended use was relief of communicating hydrocephalus, it can also be used in the treatment of rhinorrhea, bulging craniectomy sites, and postsurgical lumbar pseudomeningoceles (2). A combined series of 107 lumboperitoneal shunting procedures have been performed, including several for cases of otorrhea, spinal-subclavicular fistula, and pseudotumor cerebri, and the experience has been evaluated.

Materials and Methods

Patient Population

We tested 82 cases of communicating hydrocephalus; the diagnosis had been confirmed by computerized tomography and/or radionucleotide scanning. Five patients were worked up for pseudotumor cerebri. The 20 spinal fluid fistulae included leakage from the nose in 17 patients: 11 posttraumatic cases, 5 cases following transphenoidal hypophysectomy, and one instance of spontaneous rhinorrhea. Two patients with otorrhea had basilar skull fractures. One spinal-subclavicular fistula developed after removal of a Pancoast tumor. All of the cases of cerebrospinal fluid leakage were observed for at least 10 days before undergoing the shunting procedure.

Equipment

The Spetzler shunt is available from Heyer-Schulte Co. (Goleta, CA) as a one-piece model with perforations at the proximal end and slit valves at the distal end; no reservoir is included. A variety of devices are available to form a three-piece model with an in-line flushing reservoir that has a one-way valve. A separate miter valve may be attached with high, medium, or low pressure. Connectors and suture collars are also supplied.

Surgical Technique

The patient is placed in the lateral decubitus position with the right side elevated and the operating table flexed. A 2-cm midline incision is made between the L4 and L5 spinous processes. A 14-gauge Tuohy needle is introduced into the

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subarachnoid space with the bevel pointed cephalad. The proximal end is advanced into the thecal sac for a distance of 8 cm. As soon as cerebrospinal fluid is observed to be coming out the distal end, the Tuohy needle is withdrawn. One suture collar is used to prevent displacement of the shunt from the spine. A 2-cm incision is made in the right flank, and a malleable passer is employed to deliver the distal end of the shunt. If a line-flushing reservoir is needed, the device is inserted and buried under the subcutaneous fascia. A 2-cm incision is made in the lower right quadrant of the abdomen, and the same passer delivers the tubing (Figure). Another suture collar prevents dislodging of the tubing. The fibers of the rectus abdominis are spread, and a blunt trocar is used to insert the distal end into the peritoneal cavity. In the cases of spinal fluid fistula, the slit valves are cut off prior to insertion in order to insure maximum flow. All the incisions are closed in two layers with 4-0 nonabsorbable sutures.

Results

In the cases of normal pressure hydrocephalus, the symptoms of dementia, ataxia, and incontinence were noticeably improved in 80% of the patients. All the patients with pseudotumor were free of papilledema postoperatively. Every cerebrospinal fluid fistula resolved within 48 hours of shunt implantation. Two shunts had to be revised following displacement from the spinal subarachnoid space. One distal tubing was displaced from the peritoneum into the subcutaneous tissue. There was one wound infection, which was treated with nafcillin, and one infection secondary to abdominal exploration.

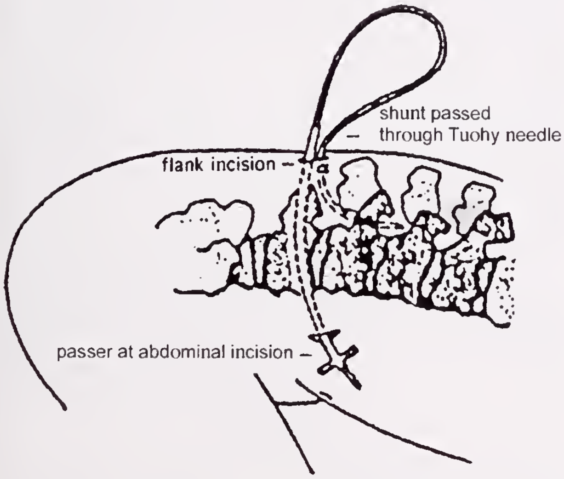
shunt passed through Tuohy needle
flank incision
passer at abdominal incision

Figure. Artist's drawing of surgical insertion of lumboperitoneal shunt.

Discussion

Additional clinical application for cerebrospinal fluid leakage following removal of a leptomyelolipoma was reported by James and Tibbs (3) in 1981. In 1982, Katz et al. (4) published successful shunting of a spinal-subclavicular fistula following thoracotomy. Others have reported their experiences with the use of percutaneous lumboperitoneal shunting for rhinorrhea (5–7), chronic hydrocephalus (8), and pseudotumor cerebri (9, 10). Aoki (11) found that the incidence of infection (1%), obstruction (14%) and other malfunctions (2%) was significantly less with the percutaneous technique of lumboperitoneal shunting than that found with ventriculoperitoneal shunts.

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Endoscopic Carpal Tunnel Release:

Report of 146 Cases

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Abstract

Objective: The purpose of this study is to describe one type of surgical treatment of carpal tunnel syndrome, namely endoscopic carpal tunnel release.
Materials and Methods: One hundred forty-six (146) cases of median nerve compression underwent the same-day procedure.
Results: Eighty-six percent (86%) were favorable, and 14% unfavorable. There was no damage caused to nerves, vascular structures, or tendons.
Conclusions: Although overall long-term results of endoscopic carpal tunnel release appear similar to those of open release, patients who undergo endoscopic carpal tunnel release demonstrate a quicker functional recovery, less postoperative pain, and less scarring than open carpal tunnel release patients.
Key Words: Carpal tunnel syndrome, transverse carpal, ligament, endoscopic carpal tunnel release, open carpal tunnel release.

Introduction

Carpal tunnel syndrome (CTS) is perhaps the most commonly studied of all entrapment neuropathies. Sir James Paget (1) is credited with the first report (in 1854) of its clinical manifestations following the healing of a distal radius fracture in a patient. Subsequently, in 1880, James Putnam described patients who complained of "numbness, reoccurring periodically, coming on especially at night or very early in the morning and affecting one or both hands" (2, 3). Although similar clinical reports appeared later in the literature, the entity was largely ignored until 1950, when Phalen (4) described the syndrome as due to "compression of the median nerve beneath the transverse carpal ligament" (TCL). He also made note of the significance of Tinel's sign, a percussion of the median nerve at the wrist, producing tingling in the hand. A second test, which has become known as Phalen's test, reported hand tingling caused by prolonged wrist flexion.

Methods

This study involved a total of 128 patients with electrodiagnostically proven CTS. One hundred ten (110) patients had unilateral disease and 18 patients had involvement of both hands. The disease in this group of patients was more prevalent in females (63%). The age range was 22–86, with an average age of 51. Eighty-five (85) cases (58%) were of the right hand, 61 were of the left (42%). One hundred two (102) cases (70%) included sleep disturbances. Sixty-six (66) (45%) were compensation cases, of which 25 (17%) involved computer keyboard operators.

Between June 1993 and September 1998, 146 procedures of endoscopic carpal tunnel release (ECTR) were performed upon the 128 patients, utilizing the Brown technique (5), a modification of the two-portal Chow technique (Figure). The procedure was performed with local anesthesia, using approximately 3 cc of lidocaine with epinephrine injected into the two portals. A tourniquet was used in all cases, with an average tourniquet time of 11 minutes.

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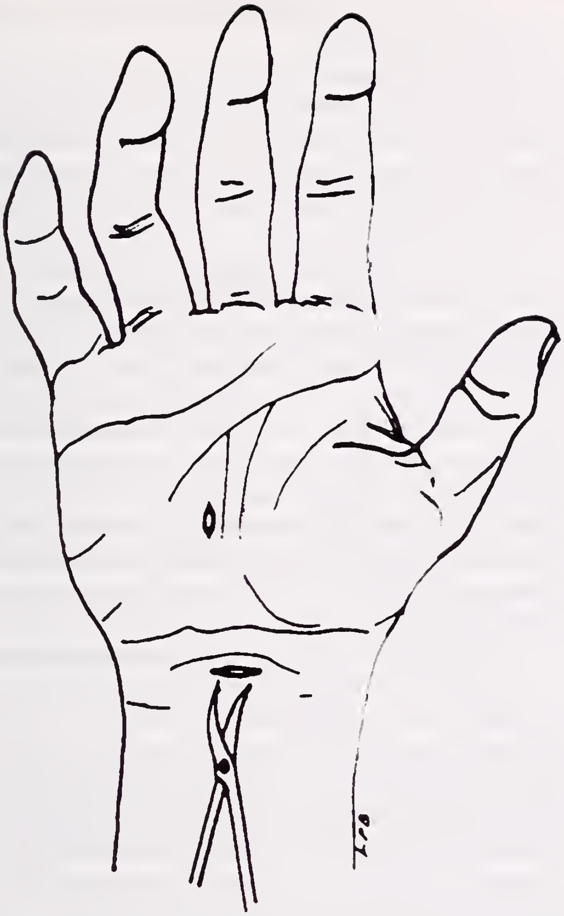

Figure. Two-portal technique with one small incision just proximal to wrist crease, second incision mid-palm.

Electrodiagnostic Evaluation

Positive nerve conduction findings included slowing of the median sensory nerve action potentials, the most sensitive sign of abnormality (6). In addition, a decrease in amplitude or, in severe cases, the absence of the sensory nerve action potential was found. Prolonged latencies of the median-nerve compound muscle action potentials and reduction in amplitude or conduction velocities were also found. Needle electromyography (EMG) is less useful for CTS diagnosis and is rarely positive. When EMG abnormalities are noted, they may indicate advanced and chronic axonal denervation, or they may lead to consideration of alternate diagnoses (7).

Results

There were two categories of results, as described by the patients: (a) complete or significant relief of symptoms, 126 (86%), and (b) partial or no relief of symptoms, 20 (14%). No patient claimed to have been worsened by the surgery. There were no cases of wound infection, nerve damage, vascular damage, tendon laceration or reflex sympathetic dystrophy. No patients complained of recurrence of symptoms after having obtained relief. One interesting finding was that all 102 cases (70%) in which patients complained of sleep disturbances fell into category "a". This would suggest that sleep disturbance may be a good prognostic sign for ECTR. Return to work varied from 4 – 32 days, averaging 16 days. Office workers averaged 12 days, manual laborers 25 days. In 212 cases of open carpal tunnel release (OCTR) seen by one of the coauthors prior to 1993, the patients returned to work on the average within 37 days. Postoperative pain and scarring were less of a problem than in OCTR patients, probably due to this being a less invasive procedure. The principal complication encountered in this series was failure to improve after surgery, which occurred in 14% of the cases.

Discussion

Signs and Symptoms

Most patients with CTS present with complaints of numbness and tingling in the thumb, index, middle, and radial half of the ring fingers. It is quite common, however, that the entire hand may show sensory disturbances due to a defective vasomotor reflex (8) or autonomic nerve dysfunction (9). Paresthesias may radiate to the elbow, or even the arm or shoulder. Numbness and tingling frequently waken the patient from sleep at night. Wrist pain, also common, occurs after repetitive motions or prolonged wrist flexion or extension. In advanced cases, weakness of the hands and wrists may be reported, and patients frequently complain of dropping objects or having difficulty opening jars or turning doorknobs. Thenar atrophy may be seen in chronic cases.

Epidemiology and Associated Conditions

CTS is most frequently seen in women, with the majority of cases between the ages of forty and sixty (10). Although occupations requiring repetitive use of the wrists or involving heavy manual work have been associated with CTS (11), some find job-related activities controversial as a causative factor (12). Trauma, such as distal radius fracture, lunate dislocations, blunt injury to the wrist and post-traumatic arthritis, may produce structural changes leading to carpal tunnel symptoms (13, 14).

Some systemic diseases may increase the risk of developing CTS symptoms. Diabetes is frequently associated with CTS (14). Acromegaly, however, is the most common associated endocrine disorder, producing CTS symptoms in 35% of acromegalics (15). Rheumatoid arthritis, producing tenosynovitis and a space-occupying lesion in the carpal tunnel, is also a risk factor (13). Pregnant women may develop CTS, mostly in the third trimester; their symptoms usually resolve within one month of delivery (17). Other medical conditions linked to CTS are hypothyroidism, alcoholism, amyloidosis, chronic renal failure with dialysis, and space-occupying lesions such as lipomas and ganglion cysts (13, 17).

Anatomy and Pathophysiology

The carpal tunnel is bounded by the thick TCL as the roof anteriorly, and the carpal bones as the floor dorsally. In its narrowest cross section, it is 2.0–2.5 cm in diameter. Through the tunnel pass nine finger flexors (four flexor digitorum superficialis tendons, four flexor digitorum profundus tendons, and the flexor pollicis longus tendon) along with the median nerve. The TCL is 3 cm long, extending from the level of the distal wrist crease into the palm, where it terminates in a sharp fibrous edge. Proximally, the TCL is continuous with and a thickening of the volar forearm fascia.

In flexion of the wrist, the median nerve is compressed against the TCL. During both flexion and extension, moreover, pressure within the carpal tunnel increases (18). As a result, it has been hypothesized (19, 20) that compression forces within the tunnel lead to mechanical deformation and eventual demyelination of the median nerve, as well as ischemic changes to the nerve.

Treatment

Treatment may be conservative or surgical. Conservative treatment consists of avoidance, job modification, splinting, anti-inflammatory agents, observation and other, less conventional forms of treatment. Avoidance involves abandoning or modifying tools which seem to cause or exacerbate symptoms, such as jackhammers, splicing tools and heavy wrenches. Station or job modification may be implemented by (for example) adjustment or padding of keyboards. Splinting is helpful mainly to relieve night symptoms, maintaining the wrist in a neutral position and making it easier for the patient to avoid unconscious wrist movements during sleep. However, splints eventually tend to lose their effectiveness as the symptoms of CTS worsen.

Nonsteroidal anti-inflammatory drugs (NSAIDs) may afford some relief, but they never fully relieve symptoms. The use of Vitamin B6 for CTS is not clearly beneficial. Steroid injections, popularized by Phalen (20), are now rarely used.

Observation and symptomatic treatment are helpful in cases associated with pregnancy, obesity, diabetes or rheumatoid arthritis, as the CTS may be relieved by the resolution or improvement of the associated conditions. Other forms of treatment, such as "stretching techniques," physical therapy and occupational therapy appear to be largely ineffective. Overall, conservative methods seem most helpful in mild cases, but have little, temporary, or no effect on cases of CTS in which the symptomatology is severe (21).

Surgical release may be performed by open or endoscopic techniques. OCTR, popularized by Phalen in the 1950s, is a conventional, well-established operation, of which there are two types. The first consists of open division of the TCL. The second type adds exploration, epineurectomy and neurolysis of the median nerve through the same incision (22). Results of open surgical release are time tested and well proven.

ECTR, introduced independently by Chow (23) and Okutsu (24) in 1989 has gained a great deal of popularity in the past decade; it is performed through one portal or two portals. The basic idea of ECTR is to introduce a fenestrated cannula deep into the TCL through a small skin incision at the wrist, and then divide the TCL under endoscopic visualization. This technique requires a good deal of endoscopic expertise, and because of the high learning curve involved, is fraught with more potential complications than OCTR. The controversy between proponents of OCTR and ECTR has been ongoing since the early 1990s.

Complications

Nationally, there have been reports of major complications after using ECTR including median nerve, ulnar nerve and digital sensory nerve lacerations, as well as tendon lacerations and vascular injuries to the superficial palmar arch. Incomplete division of the TCL, reflex sympathetic dystrophy, and infection have also been reported (5, 25). Most of these complications can be attributed to the relatively high learning curve involved in ECTR.

Conclusions

ECTR is a delicate and effective procedure. Although it remains controversial, mainly because of its steep learning curve for surgeons and early reports of complications, it has gained wide acceptance among orthopedic surgeons and hand surgeons who are skilled endoscopists. In a series of 146 consecutive cases, the authors found a favorable result rate of 86%, with no major complications. Patients with sleep disturbances appear to have a more favorable prognosis for a good surgical outcome. As compared to OCTR, ECTR seems to offer a quicker functional recovery and earlier return to work, as well as less postoperative pain and scar formation. Long-term outcomes, however, appear to be similar with both techniques. We believe that ECTR should be performed only by experienced endoscopists, arthroscopists and hand surgery specialists familiar with endoscopy.

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Percutaneous Microdecompressive Endoscopic Cervical Discectomy with Laser Thermodiskoplasty

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Abstract

Objective: To study the surgical outcome of outpatient percutaneous microdecompressive endoscopic cervical discectomy with lower energy laser for shrinkage of disc material (thermodiskoplasty).
Method: Since 1994, 200 patients with herniated cervical discs have presented at the authors' clinic, with unilateral radicular pain. The diagnosis was confirmed by MRI or CT, and EMG.
Results: At an average follow-up of 25 months, 94.5% of the cases had good-to-excellent results. Eleven patients (5.5%) remained symptomatic, with persistent neck and upper extremity pain associated with paresthesias. There were no significant postoperative complications. Average time before returning to work was 10 days.
Conclusions: Percutaneous microdecompressive endoscopic cervical discectomy with laser thermodiskoplasty has proven to be a safe and efficacious minimally invasive procedure.
Key Words: Percutaneous microdecompressive endoscopic cervical discectomy, laser thermodiskoplasty, minimally invasive surgery.

CONVENTIONAL OPEN CERVICAL DISCECTOMY, with or without bony fusion, is considered the standard treatment for cervical disc protrusion (1). However, open discectomy with fusion is associated with significant local inflammation, graft donor site pain, and a lengthy period of convalescence (2, 3). In contrast, percutaneous microdecompressive endoscopic cervical discectomy (4) is minimally invasive and offers decreased morbidity, requires no bone graft (a cause of secondary symptoms) and promises a shorter recuperation. The purpose of this study is to evaluate the surgical outcome of outpatient percutaneous microdecompressive endoscopic cervical discectomy with lower energy laser for shrinkage of disc material (thermodiskoplasty).

Materials and Methods

Patient Population. Since 1994, 200 consecutive patients (26–72 years of age) with 360 nonextruded cervical disc herniations have presented at the authors' clinic. The levels of involvement were 1 at C2–3, 34 at C3–4, 92 at C4–5, 104 at C5–6, 127 at C6–7, and 2 at C7–T1. The indications for surgery were: (a) neck pain with radiation down the arm; (b) symptoms and signs of sensory loss, tingling, numbness, muscle weakness, and/or decreased deep tendon reflexes; (c) MRI or CT findings of nonextruded disc herniation consistent with the signs and symptoms; (d) positive electromyography and/or nerve conduction studies; and (e) no improvement after 12 weeks of conservative therapy.

Preoperatively, non-steroidal anti-inflammatory agents were given to all of the patients. Thirty cases (15%) were treated with epidural steroid injections, 25 (12.5%) with oral steroids, 74 (37%) with muscle relaxants, 35 (17.5%) with aspirin, 10 (5%) with tranquilizers, and 64 (32%) with narcotics or prescription analgesics.

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Some patients received more than one form of treatment.

The contraindications to any surgical intervention were acute or progressive degenerative spinal cord disease and neurological or vascular pathologies mimicking a herniated disc. Since 1994, 42 other patients underwent open cervical operations for (a) advanced spondylosis with disc space narrowing, (b) significant bony spurs that could block percutaneous entry into the disc space, (c) cervical spinal canal stenosis or lateral recess stenosis, and (d) an extruded disc or free fragment.

Surgical Technique. Under local or general anesthesia, the patient was placed in a supine position with the neck extended by placing a rolled towel under the shoulders. A soft strap was placed over the forehead for stabilization. The shoulders were gently distracted downward with tape. C-arm fluoroscopy was used in anteroposterior and lateral planes to direct the placement of a spinal needle onto the disc surface. Initially, at the point of entry adjacent to the medial border of the right sternocleidomastoid muscle, firm pressure was applied digitally in the space between the muscle and the trachea and pointed toward the vertebral surface. The larynx and trachea were displaced medially and the carotid artery laterally. The esophagus was made more prominent with the insertion of an endotracheal tube. The pulse of the carotid artery was augmented with sympathomimetics. The anterior cervical spine was palpated with the fingertips, and a #18-gauge spinal needle was passed into the disc space. The position was confirmed fluoroscopically.

A 2–3 mm skin incision was made, and a narrow guide wire was passed through the needle. The needle was then removed. A blunt trocar was introduced over the guide wire down to the interspace, followed by a cannula. A trephine inserted through the cannula cut the annulus in a circular fashion. Minicurettes loosened and removed disc material prior to introduction of a suction-irrigation system and the discetome with a guillotine-cutting blade (Fig. 1). The instruments included a probe, grasper forceps, and laser fiber (Fig. 2). Movement in a critical fan sweep maneuver, a 25° rocking excursion of the cannula hub from side to side, increased the removal up to a 50° cone-shaped area within the disc space (Fig. 3). The procedure was closely monitored with the fluoroscope (Fig. 4) and an endoscope (Figs. 5A, B). The holmium: yttrium-aluminum-garnet laser with right angle or side-fire probe facilitated the discectomy. In addition, nonablative levels of holmium laser energy (500 joules) or thermodiskoplasty added shrinking of collagen and fibrocartilage; the tightening effect further decompressed and hardened the herniated cervical disc.

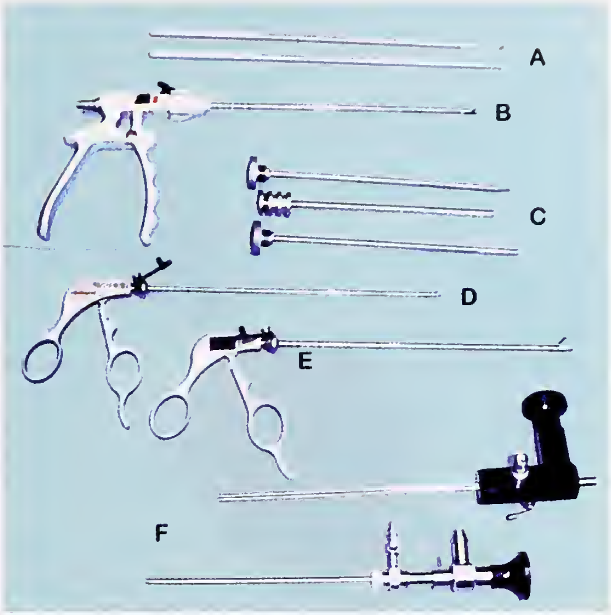

Fig. 1. Minimally invasive spine surgery instruments: **(A)** minicurettes, **(B)** discectome, **(C)** discectomy dilator/cannula/trephine, **(D)** cutter forceps, **(E)** grasper forceps, and **(F)** endoscopes.

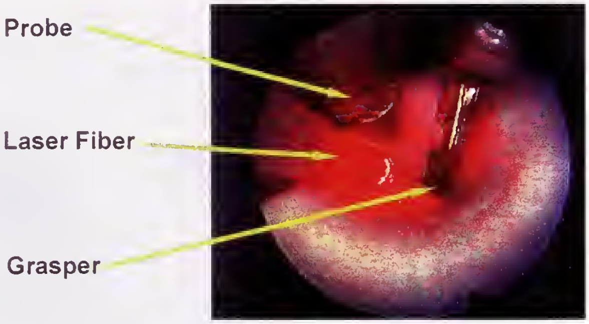

Fig. 2. Three microdiscectomy instruments working inside of disc space.

Results

Preoperative MRI (Fig. 6A) reveals a bulging herniated disc. Fig. 6B illustrates postoperative changes in this disc space. Follow-up averaged two years, with a range of 9–45 months. Eleven patients (5.5%) had persistent slight-to-mild neck and upper extremity pain that required analgesic medication, while 189 (94.5%) had good-to-excellent recovery with minimal or no pain and resumption of a fully active lifestyle. There were no postoperative complications of wound infection, or arterial or nerve compromise. Of the 198

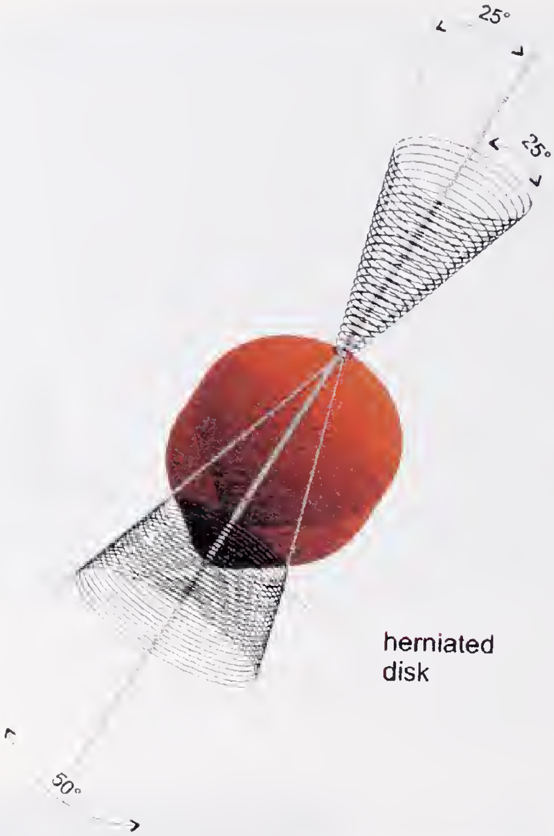

Fig. 3. Critical fan sweep maneuver in cone shape.

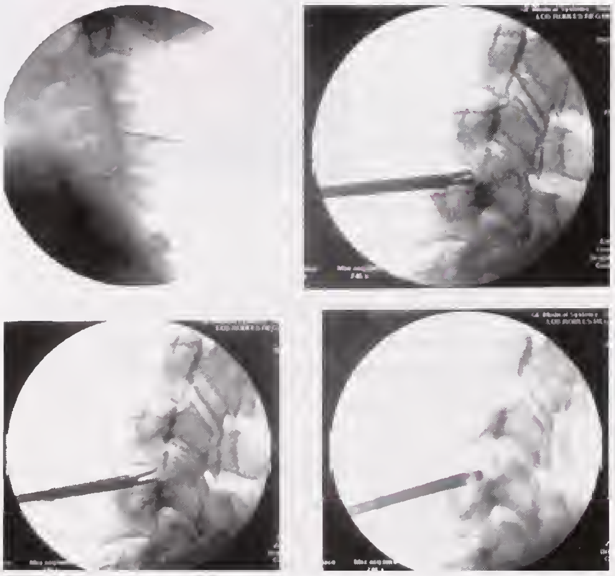

Fig. 4. X-rays of curette (upper left), cutter (upper right), grasper (lower left), and discectome (lower right) in disc space.

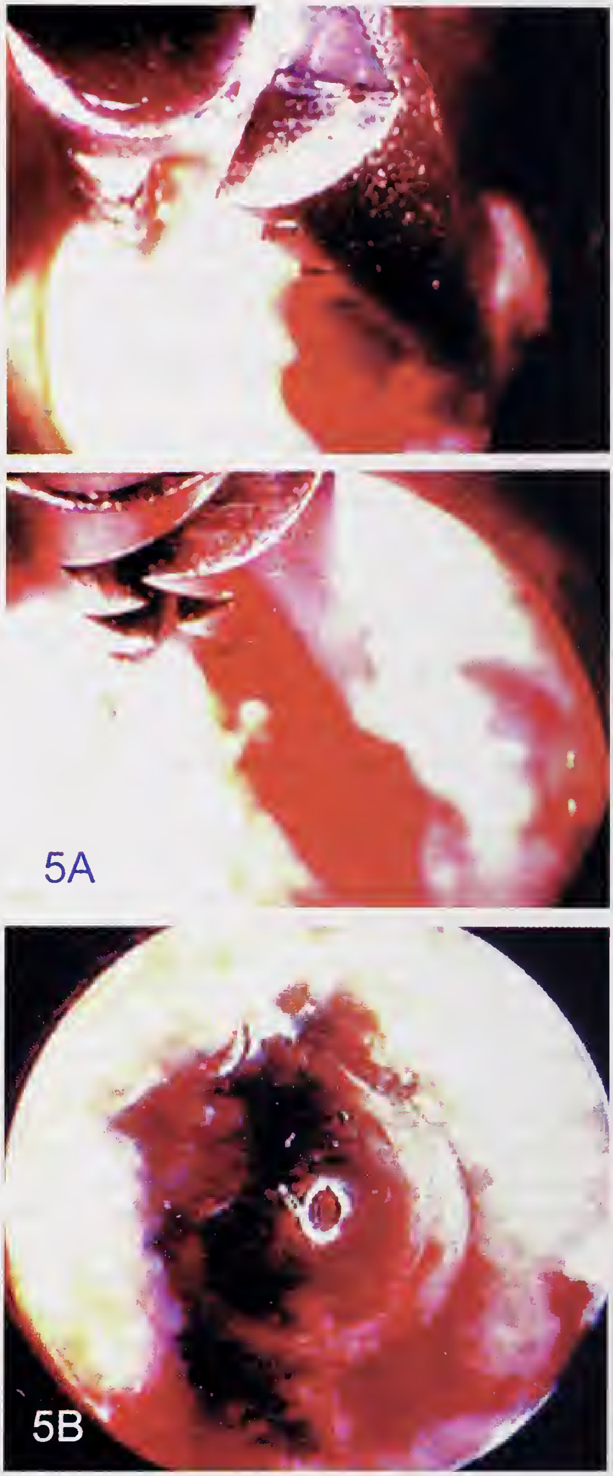

Fig. 5. **(A)** Endoscopic views of grasper removing disc material. **(B)** Note defect left following discectomy and debulking.

cases (99%) demonstrating muscle spasm preoperatively, 6 (3%) continued to be symptomatic, with some neck stiffness. All 200 patients reported dermatome-specific numbness of the upper extremities and manifested decreased pain and touch sensation; 8 (4%) reported persistent numbness and tingling and 6 (3%) had occasional diminished feeling without objective findings on neurological examination. The average time before returning to work was 10 days, with a range of 3 days to 4 weeks.

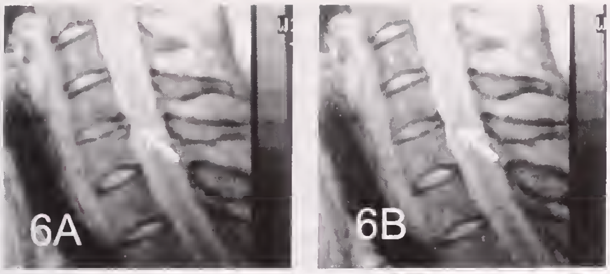

Fig. 6. **(A)** Posterior protrusion of disc. **(B)** Note shrinkage and tightening of disc material.

Discussion

The current trend of evolution of all spinal surgery has been toward less-invasive techniques. In 1964, Smith (5, 6) introduced chymopapain chemonucleolysis to treat herniated nucleus pulposus. Hijikata (7) and Onik et al. (8) described percutaneous lumbar discectomy. Ascher (9) and Sherk (10) then reported laser discectomy.

Key (11) first described the pathologic findings of two cases of cord compression by "intervertebral substance" in 1838. In the nineteenth and early twentieth centuries, reports of cervical chondromas of the cervical spine were presented. Stookey (12) described the clinical symptoms and anatomic location of cervical disc herniation in 1928. Subsequently, in 1934, Mixter and Barr (13) further implicated cervical disc protrusions. Before 1950, the standard surgical approach to discs in the upper spine was posterior cervical laminectomy. Bailey and Badgley (14), Cloward (2, 3), and Robinson and Smith (15) popularized the anterior approach with interbody fusion in the 1950s. Hirsch (1) in 1960, then Robertson (16) in 1973, recommended cervical discectomy without fusion; results and success rates similar to those with fusion were reported. Fukushima (17) introduced the ventriculofiber in 1973 and further enhanced the foundation for percutaneous endoscopic cervical discectomy (18).

The advancements in miniaturization of microsurgical instrumentation, fiber optics, improved fluoroscopic imaging, high-resolution digital video imaging endoscopy, accumulated experience in percutaneous lumbar discectomy (4, 19–24), and the application of lasers to surgery (9, 10, 17, 25–27) have all facilitated the development of percutaneous endoscopic decompressive cervical discectomy. The development of rigid and flexible endoscopes has provided better visualization of the spinal canal and disc anatomy.

Prior to 1995, the holmium laser (Trimedyne, Irvine, CA) was used in surgery on joint ligaments, skin, and the retina. Since 1995, our method employs the holmium laser at non-ablative lower energy settings (500 joules) to achieve the triad of surgical objectives: lowering intradiscal pressure, debulking the disc, and shrinking the fibrocartilage.

Success rates reported by others (28, 29) were 40% and 77%, respectively. Our success rate of 94.5% reflects careful patient selection, thorough diagnostic evaluation by MRI, CT, and electromyography, and careful correlation with signs and symptoms. In our experience, this minimally invasive outpatient procedure has proven to be safe and effective, with less morbidity, more rapid recovery, and significant economic savings.

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Arthroscopic Microdiscectomy:

An Alternative to Open Disc Surgery

Parviz Kambin, M.D.[1], And Martin H. Savitz, M.D.[2]

Abstract

Objective: To assess minimally invasive spinal surgery under endoscopic magnification and illumination (arthroscopic microdiscectomy) as a reliable alternative to open microsurgery for most herniated lumbar discs.
Method: A total of 600 cases are evaluated retrospectively in terms of patient selection and technique. One series of 300 operations was performed by a key academician in the development of arthroscopic microdiscectomy. A second series of 300 patients was treated by a neurosurgeon in private suburban practice.
Results: In terms of patients self-evaluation, satisfactory outcome rates of 85 – 92% were realized. The patients considered brief intravenous anesthesia and same-day scheduling preferable to general anesthesia and hospitalization needed for open laminotomy and discectomy. Fewer than 2% of the cases required a second surgery.
Conclusion: The authors are of the opinion that advantages include: (1) one-hour operative time, (2) negligible blood loss, (3) avoidance of significant scarring in the spinal canal, and (4) anterolateral fenestration of the annulus for continuing relief of intradiscal pressure and nerve root decompression.
Key Words: Arthroscopic microdiscectomy, fluoroscopy, laser, percutaneous discectomy, endoscopy, lumbar spine.

Introduction

Ottolenghi and Argentina (1) in 1955 and Craig (2) in 1956 described posterolateral biopsy of the spine. A similar technique was used for discography (3) and chemonucleolysis (4). In 1942, Poole (5) had already employed a modified cystoscope for percutaneous endoscopy of the subarachnoid space; 400 myeloscopic examinations of the cauda equina allowed the differential diagnosis of herniated nucleus pulposus, hypertrophied ligamentum flavum, adhesive arachnoiditis, benign neoplasm, and metastatic carcinoma. Beginning in 1973, Kambin (6) combined decompression of the spinal canal by laminectomy with introduction of a tube by posterolateral approach for evacuation of a protruding disc. Hijikata (7) in 1975 independently developed instrumentation for percutaneous debulking of the nucleus pulposus. Other percutaneous methods included medial nucleotomy by an automated aspiration probe (8) and disc vaporization by a fluoroscopically placed laser fiber (9).

The introduction of arthroscopic illumination and magnification allowed identification of the triangular "working zone" (Figs. 1A & 1B). As the spinal nerve descends diagonally across the intervertebral disc, the annulotomy site is defined inferiorly by the proximal vertebral plate, and posteriorly by the articular process of the lower segment. Departing from the foramen, the exiting root moves anteriorly, distally, and laterally, and forms the anterior boundary of the triangular working zone. Within the triangle, there is generally ample room for introduction of the coaxial instruments (Fig. 2). The initial open technique with posterolateral introduction of a tube was gradually replaced by a completely percutaneous operation employing a modified discoscope, a working sheath with a 6.4 x 6.4 mm or 6.4 x 9.4 mm outer diameter, and coring instruments and forceps designed for a 5 x 5 mm or 5 x 8 mm inner access (10).

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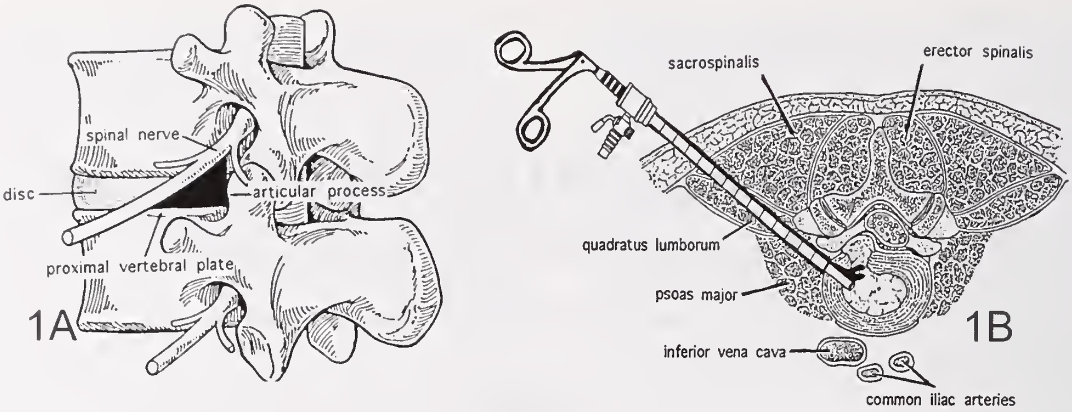

Fig. 1. Drawings depicting the operative area. **(A)** Lateral view. The black triangle represents the working zone. **(B)** Cross-sectional drawing of the anterolateral surgical approach to the disc space.

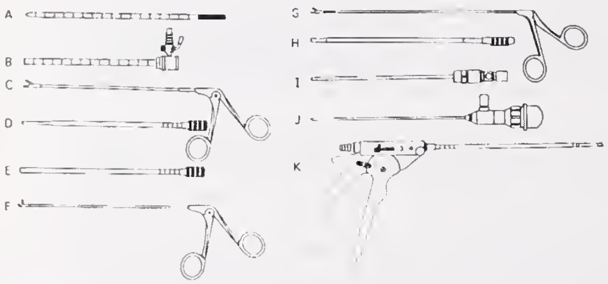

Fig. 2. Arthroscopic microdiscectomy instruments: **(A)** blunt cannulated trocar, **(B)** working sheath, **(C)** straight forceps, **(D)** small core, **(E)** large core, **(F)** upcutting forceps, **(G)** flexible forceps, **(H)** deflector tube, **(I)** power shaver, **(J)** discoscope, and **(K)** suction punch.

Savitz reported a series of 120 same-day, microsurgical, arthroscopic, lateral-approach, laser-assisted fluoroscopic discectomies (1). In 1996, the neodymium:yttrium-aluminum-garnet (Nd:YAG) laser, which had been confined to hemostasis, was replaced by the holmium: yttrium-aluminum-garnet (Ho:YAG) laser, manufactured by New Star Lasers, Inc. (Auburn, CA) and approved by the FDA for disc vaporization. A portable unit allowed the procedure to be scheduled at three community hospitals in two suburban counties within a 25-mile radius of New York City.

Patient Selection

Initially, ideal cases were defined as having: (1) symptoms for up to 6 months of unilateral sciatica which responded to rest; (2) mechanical signs of nerve root irritation when erect; and (3) one protruding or prolapsed disc having positive tension signs, as interpreted by CT or MRI. In addition to disc extrusion, there were other factors considered nonideal for percutaneous endoscopic discectomy. Unrelieved foraminal compression due to segmental spondylosis is a known cause of failed back syndrome. Cauda equina syndrome is considered an indication for urgent open decompression of the nerve root. Prior disc surgery is often complicated by scar tissue in the spinal canal which is not resected by arthroscopic technique. Obese patients do not fit easily on the radiolucent frame, and their spinal anatomy is difficult to visualize on fluoroscopic imaging. Diabetic neuritis and neuropathy can mimic the signs and symptoms of a herniated nucleus pulposus. Inaccessibility was defined in some individuals with a central herniation or an elevated iliac crest.

The diagnosis was made by computerized tomography, magnetic resonance imaging, and/or myelography. Half of the cases had undergone two neuroradiologic studies. The patients selected fell into 3 categories: (a) disc prolapses occupying up to 50% of the spinal canal (Fig. 3 left), (b) extremely lateral disc herniations (Fig. 3 middle), and (c) lateral recess stenosis with sequestered but not migrated herniation (Fig. 3 right). All of the cases were studied retrospectively.

Unilateral Technique

With the patient positioned prone on a radiolucent frame suitable for fluoroscopy, the skin entry site was 8 – 12 cm from the midline. Insertion of a spinal needle at about 45°, followed by a guide wire, cannulated obturator, and working sheath at the triangular working zone, was accomplished by C-arm monitoring (Fig. 4). Prior to annulotomy by circular coring instruments, the safety of the nerve root was ascertained. In order to confirm the posterior positioning of the instruments, dorsal and ventral tilting of the medial end of the cannula were carried out. Repeated perforation of the annulus with the spinal needle demonstrated correct placement of the working sheath on the disc space. Visualization of annular

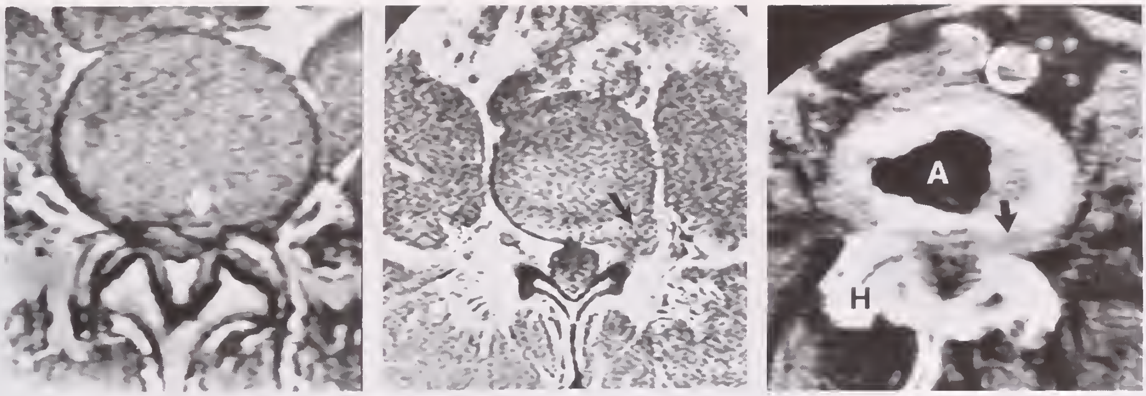

Fig. 3. Preoperative neuroradiologic studies: **Left:** MRI demonstrating disc herniation (arrow) into left lateral recess. **Middle:** MRI showing left foraminal herniated disc (arrow) compressing the exiting nerve root. **Right:** CT showing air (A) consistent with degenerative disc disease, superimposed facet hypertrophy (H) causing stenosis and asymmetrical disc protrusion (arrow) extending to the left lateral recess.

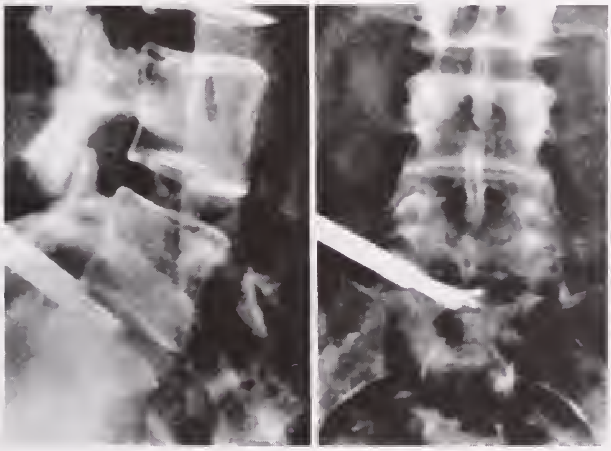

Fig. 4. Intraoperative photographs taken via the fluoroscopic image intensifier. **Left:** Lateral view showing the working sheath resting on the annulus and a small circular cutting instrument within the disc space. **Right:** Anteroposterior view showing the working sheath aligned with the midpart of the pedicle and flexible forceps delivered within the disc space by a deflector tube.

fibers and periannular adipose tissue (Fig. 5A) further assured the absence of any part of the spinal nerve within the operative field. Removal of disc material was accomplished manually with a straight forceps and an upcutting forceps. The flexible forceps used in conjunction with a deflector tube (Fig. 3) allowed access to subligamentous and interannular fragments. A suction punch forceps and an automated shaver employing irrigation were also available. After removing 2–5 g of degenerative disc and completing the discectomy, the arthroscope showed the cavity created (Fig. 5B).

Bilateral Biportal Technique

Two working cannulas were inserted into the intervertebral disc from the left and right paramedial approaches (Fig. 6). The arthroscope was introduced through one portal to visualize the forceps, suction punch, and automated shaver being manipulated through the second portal. Under direct illumina-

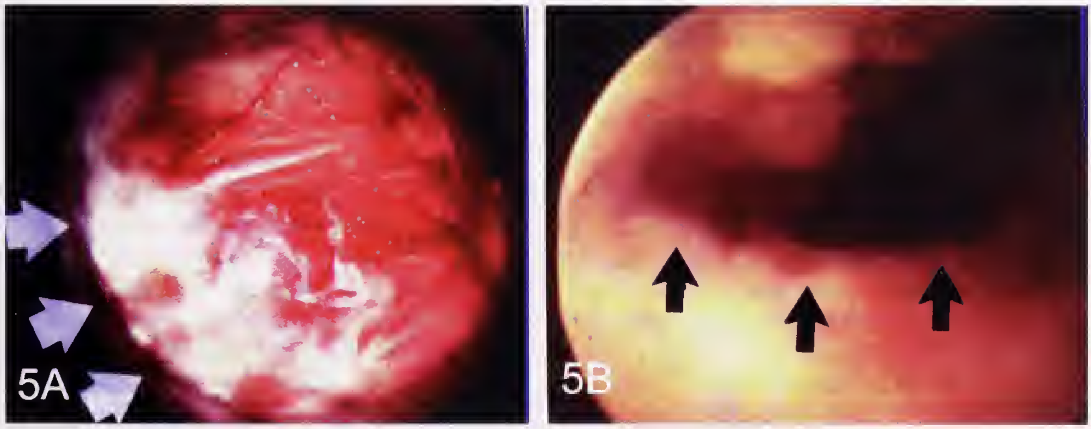

Fig. 5. Intraoperative photographs, arthroscopic views: **(A)** Loose fatty tissue (arrows) prevents unobstructed inspection of annular fibers. **(B)** Appearance of the cavity (arrows) created behind the annulus.

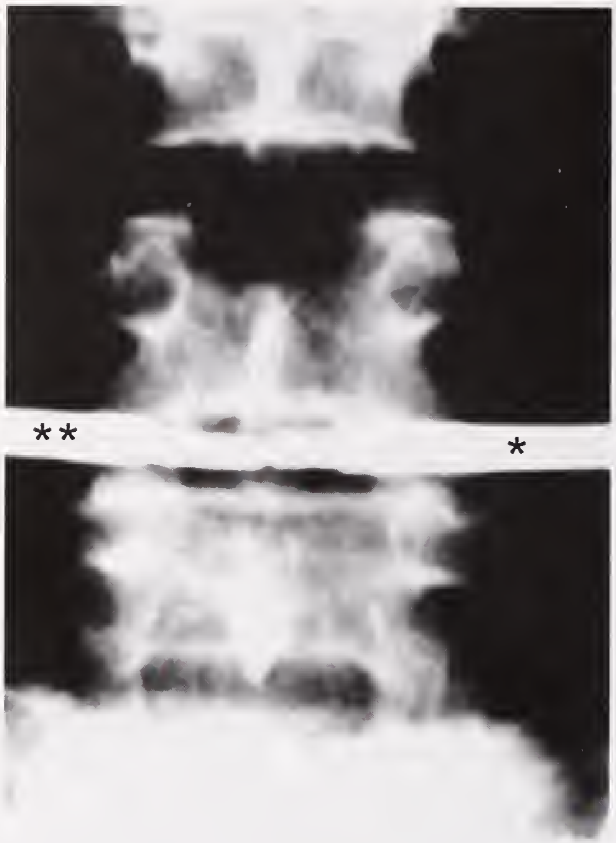

Fig. 6. Intraoperative photograph taken via the fluoroscopic image intensifier. Anteroposterior view showing the point of contact inside the intervertebral disc with the discoscope (*) inserted from one side and the deflecting suction forceps (**) from the opposite side.

tion and magnification, the posterior longitudinal ligament can be identified; the dural sac can be exposed for retrieval of intracanalicular fragments (Fig. 7).

Laser Annular Hemostasis

Kambin (12) employed a radiofrequency coagulator, while Savitz (11) preferred a laser, to stop any bleeding from small vessels in the annulus. A working discoscope allowed video monitoring of the laser fiber. On settings of 17–21 watts and 1.5-second pulses, the Nd:YAG laser was shown to cause hemostasis to take place suddenly and without predictability as the wattage was increased (Fig. 8A). The Ho:YAG laser provided more limited areas of charring (Fig. 8B) and had the added safety feature of audio feedback with settings of "CONTINUOUS" and 5–10 pulses per second.

Anesthesia

The neuroleptanalgesic agent, either fentanyl or midazolam, was generally selected by the anesthesiologist. Xylocaine was employed for infiltration of the skin and the annulus. A nasal cannula for oxygen, pulse oximeter, blood pressure monitor, and continuous EKG were regularly in use. Conscious sedation produced a comfortable, cooperative, and amnestic patient for positioning of the working sheath, coring of the disc space, insertion of the instruments, and simple questioning: "Is the pain now in your back or your leg?" and "Can you move your toes, your ankle, your leg?" Kambin (10) performed a small number of procedures while the patients were under general or spinal anesthesia.

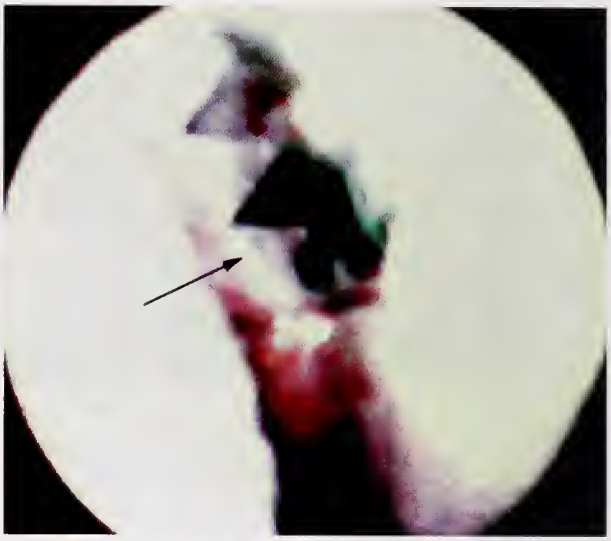

Fig. 7. Deflecting suction forceps (arrow) reaching the subligamentous region.

Outcome Data

Kambin's reported series (12–16) and Savitz's reported series (11, 17, 18) now include more than 600 patients. In terms of patient self-evaluation, satisfactory outcome rates of 85–92% were realized. The patients considered brief intravenous anesthesia and same-day scheduling preferable to general anesthesia and hospitalization necessary for open laminotomy and discectomy. Fewer than 2% of the cases required second surgery.

Complications

One transient peroneal palsy attributed to restraining straps for the operating table and one postoperative wound infection which responded to appropriate antibiotics occurred in Kambin's (15) series. In 175 consecutive patients, Kambin recorded 5 incidents of postoperative causalgic-type pain. Savitz (11, 18) reported one psoas muscle hematoma resulting in transient weakness and a 5% incidence of sympathetic mediated pain (SMP); one additional

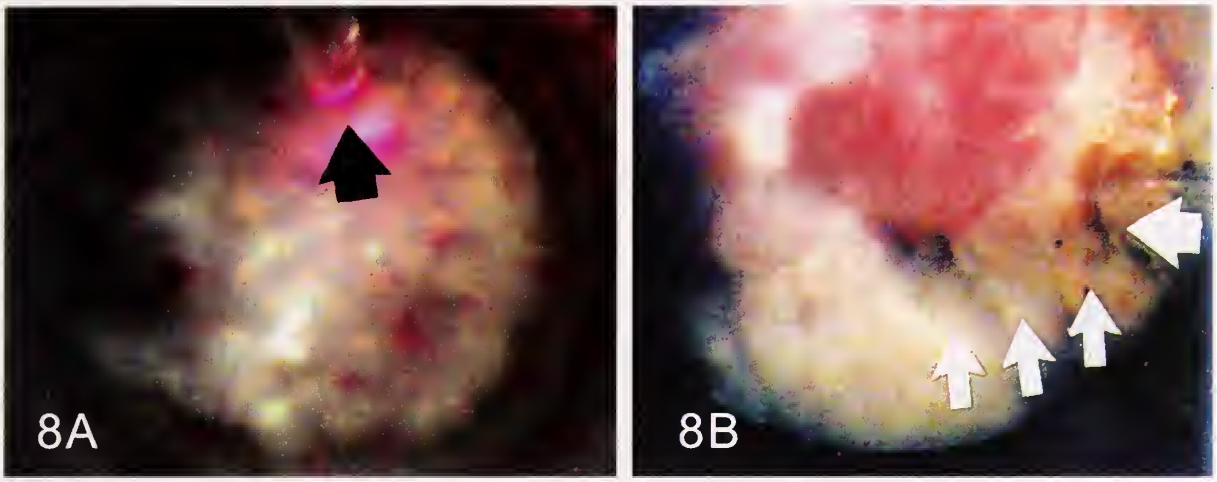

Fig. 8. Intraoperative photographs, arthroscopic view. **(A)** Diffuse charring caused by Nd:YAG laser fiber (arrow). **(B)** Ho:YAG laser (large arrow) producing areas of localized hemostasis (small arrows).

case of unilateral L5 radiculopathy following discectomy at L1–2 has not been previously reported.

SMP may occur with any injury or surgical manipulation of a peripheral nerve (19). Kambin's patients responded to steroids or nonsteroidal anti-inflammatory drugs. Alpha-blockers were administered to, and sympathetic blocks performed in, those patients of Savitz who developed SMP 4–7 days after surgery. The mechanism and cause of SMP in patients undergoing percutaneous endoscopic discectomy remain unidentified and poorly understood. More recently, Kambin (15) has been employing local delivery of 1 cc of fentanyl mixed with 3 cc of saline in the periannular region as soon as the spinal needle is in place. In addition, avoidance of vibratory disc resecting instruments has virtually eliminated the complication.

Conclusions

Proper patient selection includes careful review of preoperative imaging studies and assessment of radiculopathy and radiculitis if outcomes comparable to that of open laminotomy are to be obtained. Same-day scheduling, negligible blood loss, avoidance of general anesthesia, and minimizing scar tissue all lead to satisfactory outcomes as judged by the patients themselves. The authors are of the opinion that percutaneous endoscopic discectomy belongs in the armamentarium of every spinal surgeon.

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Percutaneous Stereotactic Radiofrequency Thermal Rhizotomy for the Treatment of Trigeminal Neuralgia

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Abstract

Background: Trigeminal neuralgia (TN) is the most common cephalic neuralgia in people over the age of fifty, with a mean incidence of 4 per 100,000. Percutaneous stereotactic differential radiofrequency thermal rhizotomy (RTR) is a well-recognized surgical treatment for TN. The purpose of this study was to evaluate a management algorithm for TN and to evaluate the effectiveness of RTR for TN after failure of pharmacologic management.
Methods: Two hundred and fifty-eight (258) patients underwent RTR from 1992–1996 and were prospectively evaluated. These patients were characterized by age, sex, side of the face and division(s) involved. Patients were evaluated for pain relief, recurrence requiring or not requiring re-operation, and the type and rate of complications. They were followed by serial clinical evaluation and telephone interview. Patients were grouped according to results: (A) Successful Result — excellent or good pain relief; (B) Unsuccessful Result — fair, poor or no pain relief. The RTR group was compared to historical controls. Follow-up ranged from 12–80 months (mean = 38 months).
Results: At early follow-up (defined as median postoperative period up to 6 months), pain relief that was excellent or good (successful results) occurred in 224/258 (87%). At long-term follow-up (> 6 months) recurrence of tic pain required re-operation in 31 patients (12%). In 37 patients (14%), recurrence of tic pain did not require re-operation. Dysesthesia developed in 20 patients (8%); corneal analgesia developed in 8 patients (3%). "Anesthesia dolorosa" developed in 5 patients (2%) and was medically managed. At the conclusion of the long-term follow-up period, 214/258 patients (83%) had excellent to good pain relief (successful result). There were no mortalities, no significant morbidity and a low rate of minor complications.
Conclusion: With the use of this specific diagnostic and management algorithm, patients with TN can be successfully managed with RTR. **Key Words:** Radiofrequency thermal rhizotomy, surgical treatment, facial pain.

Introduction

TRIGEMINAL NEURALGIA (TN) is one of the most painful and debilitating diseases known. A review of the history of TN illustrates the devastating impact that the disease has on afflicted individuals. The cause(s) of TN, as well as its medical and surgical treatments, have undergone considerable evolution (1, 2).

Trigeminal neuralgia was not well described in ancient medicine, and not until the eleventh century did the first description of this problem reach the medical literature (1). These early accounts described "severe spasms of facial pain, without loss of power or sensation." The relationship of the pain to "the jaws" and "the roots of the teeth" was also noted. At that time, one of the recommended treatments was "wine and rest in a darkened room," a home remedy not uncommon today.

The first narrative of this disease dates back to the 1671 description by a German physician, Johannes Laurentius Bausch, who suffered from a lightning-like pain in the right face (1). He became unable to speak or eat properly and finally succumbed to malnutrition. A French physician, Nicolaus André (1756), is credited

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with providing the first comprehensive description of TN as a clinical entity and first applied the name "tic douloureux" to the disorder (3). His first patient had previously had several teeth extracted without relief of pain, in an attempt to treat an infection of the maxilla. Following the last extraction, André wrote:

> . . . what had been regarded as the end of a mild and tolerable ailment, became the source of the sharpest and most uncomfortable pains, I would say the start of a tic douloureux that assailed her night and day, deprived her of sleep, and forbade her some of the bodily functions necessary for life. In fact these periodic agitations became so frequent that they rarely allowed five or six minutes of peace during an entire hour; the patient could not eat, drink, cough, spit or wipe her face without renewing her pains.

In 1773, the English physician John Fothergill, in search of treatments for TN, was the first to describe the complete clinical features of the disease, including the fact that light touch was the most common trigger. He noted that TN was more common in women and the elderly (4). In 1787, Pujol stressed the point that TN is often confused with toothache, and healthy teeth are extracted unnecessarily (5). Subsequently, Chapman in 1834 observed that the pain of TN exhibits spontaneous remissions and exacerbations, and has a lancinating quality (6). In 1896, Tiffany observed and recorded, in numerous patients, the preferential involvement of the right side of the face and of the mandibular and maxillary divisions of the trigeminal nerve (7). Oppenheim and Patrick (8, 9), in 1911 and 1914 respectively, commented on the association of TN with multiple sclerosis and its occasional familial pattern. Harris, in 1940, in a study of 1,433 cases of TN, noted that bilateral TN was more common in patients who had multiple sclerosis and/or a positive family history (10).

In the 1950s, the investigations of Kugelberg and Lindblom added significantly to our historical understanding of the clinical features of TN and began a more comprehensive approach to the study of the etiology of this disease (11). They documented that the trigger zone is usually located in the perioral region and that light tactile and vibratory stimuli are the most effective triggers, while painful stimuli are generally ineffective triggers. In addition, they measured a specific latent period between the onset of a stimulus and the onset of a painful paroxysm. They also found that the attack is self-sustained once it has been initiated and that it is followed by a refractory period lasting up to several minutes.

Sir Charles Symonds, in 1949, first called attention to the fact that the presentation of TN can be somewhat "atypical" in some patients (12). These patients may start out with a diffuse, poorly localized pain which they describe as dull, aching, burning, throbbing, or crawling in nature. This pain tends to become chronic and may be associated with other historical and physical findings that differ from TN. Over the subsequent decades, numerous authors have described patients with similar clinical phenomenology and have coined equally numerous descriptive terms for craniofacial pain syndromes (13, 14).

Many craniofacial pain syndromes have long and very complex histories. Often, eliciting the correct information to make the diagnosis is time consuming and difficult, yet it is critical if the treating doctor is going to make the correct diagnosis. Trigeminal neuralgia has one of the most consistent historical presentations and physical findings of all the craniofacial pain syndromes. The age of onset, sex, location, referral pattern, duration, quality, quantity, triggering stimuli and relieving factors, as well as any associated physical phenomena, are essential parts of the history for diagnosing a craniofacial pain syndrome.

The initial attacks of pain are usually unprovoked and start spontaneously, yet some patients will experience a dull, continuous, aching pain, usually in the upper or lower jaw or teeth, that may last for days to months before the paroxysms of pain start. This has been described in some studies and termed "pre-trigeminal neuralgia," although there is still some debate as to whether this is truly trigeminal neuralgia. The paroxysms of pain are often characterized as "sharp," "electrical-like," "stabbing," "lancinating," "bolts" of pain, which last from seconds to minutes. The pain is described as the most severe pain that the patient has ever experienced. It is on one side of the face in approximately 90% of patients, but can occur bilaterally. Only in rare cases is it on both sides at the same time. It is more common in women over the age of fifty, more common on the right side of the face, and most common in the second and third divisions, but always limited to the distribution of the trigeminal system. Very often there are tactile triggers associated with the pain attacks, yet the initial onset is usually spontaneous and the subsequent bouts of pain can also be spontaneous without any tactile triggering stimulus. This phenomenon can become so profound that patients will not be able to touch their face, brush their teeth, eat, drink, talk, shave or go out on a windy day. Often patients stay at home, change their social and eating habits, lose weight and become depressed. Strangely, the pain does not usually wake patients up from sleep.

The attacks of pain are usually of very short duration, yet they often come in bouts that may last for days or weeks, with patients having a few to hundreds of severe attacks per day. These bouts of pain are often self-limiting, and remission periods frequently may be of long duration. The bouts will recur without warning and without any inciting event or injury. These episodes of pain are often seasonal and may be precipitated by temperature changes, humidity changes, pollen or other climatic conditions.

Many patients exhibit tactile trigger areas, yet these are not universal. The trigger areas of the face are more commonly found in the perioral and perinasal area, which may be due to the somatotopic organization pattern in the trigeminal brainstem complex, as well as the large cortical representation areas that the face and mouth have in the somatosensory cortex (15). The trigger areas are usually affected by very light touch and cold, which elicits the pain. Sharp stimuli or pressure may not elicit pain. As yet, the relationship(s) between the phenomena of hyperalgesia, cold hyperalgesia and allodynia, all common findings in trigeminal neuralgia, and the underlying responsible pathophysiologic mechanisms have not been established (16).

Patients with idiopathic trigeminal neuralgia do not complain of "numbness" or paresthesia of the face, or other associated phenomena, such as headache, diffuse bilateral pain, photophobia, tinnitus, anosmia, dysgeusia, neck pain, autonomic signs, or other cranial nerve abnormalities. If these or other systemic complaints are present, then further evaluation and work-up are essential.

The physical examination entails a thorough evaluation of the head and neck, with special emphasis on the neurological examination. Cranial nerve examination should be performed, with special attention to hearing abnormalities and facial nerve abnormalities. In addition, neurosensory testing of the trigeminal system should include light touch, sharp touch, various temperatures and directions, and two-point discrimination. Note should be taken of any trigger areas, and they should be appropriately mapped out. Aside from the trigger points, when present, and minimal hypoalgesia or hypoesthesia in some patients, the neurological examination is essentially normal. Therefore, in summary, the clinical criteria for a diagnosis of trigeminal neuralgia are:

1. Severe, lancinating, paroxysmal pain
2. Unilateral pain
3. Area limited to the distribution of the trigeminal nerve
4. Trigger areas
5. No sensory deficit

The diagnosis of craniofacial pain is often quite difficult due to the complexity and similarity of presenting symptoms, and the large and diverse classification schemes and categories of disease processes. Numerous classifications have been developed by different organizations in order to aid the clinician, yet these classifications are often cumbersome and confusing. In many patients, the disease presentation does not fit neatly into the classification scheme (17–19). A starting point in the differential diagnosis of craniofacial pain is separating neuralgic from nonneuralgic pain. The cephalic neuralgias are often divided into trigeminal nerve involvement and other cephalic nerve involvement, either of cranial nerve branches or of cervical plexus branches. Trigeminal neuralgia, as discussed above, has a very specific group of findings, and the diagnostic dilemma is whether it is primary (idiopathic/classical) or secondary (due to a structural lesion). The constellation of signs and symptoms with which the patient presents will dictate what further diagnostic studies are necessary before therapy is begun. These studies can include: imaging, neurophysiologic testing, psychologic testing, nerve block or muscle injections, intravenous drug administrations, lumbar puncture for cerebrospinal fluid analysis, hematologic testing and biopsy when necessary.

Our Craniofacial Pain Group has developed an algorithm for the differential diagnosis and management of craniofacial pain disorders. This algorithm incorporates historical data, physical examination data and some diagnostic testing to guide medical and surgical management strategies for patients with craniofacial pain. The current treatment of TN consists of medical and surgical therapies. Medical management consists of pharmacologic and non-pharmacologic approaches, while surgical management consists of numerous peripheral and intracranial procedures. The first line of treatment is usually medical therapy, with drugs such as carbamazepine, baclofen, gabapentin, phenytoin or clonazepam in single or combination regimens. Pharmacologic therapy is effective for many patients; however, for some these medications either fail to relieve the pain and/or produce intolerable side effects with significant medical and functional morbidity. If medical therapy is unsuccessful or not tolerated, surgical treatment should be considered.

Of the surgical procedures, Percutaneous Stereotactic Differential Radiofrequency Thermal Rhizotomy (RTR) is a well-recognized treatment for TN (20, 21). At the Massachusetts General Hospital (MGH), where this procedure was pioneered (22), RTR is the procedure of choice for patients undergoing initial surgical management. RTR is a technique of controlled thermal ablation of nerve fibers in the trigeminal ganglion or nerve root, producing loss of pain with relative preservation of touch and more complex facial sensations (23–25). The radiofrequency generator and micro-electrodes allow for precise localization with nerve stimulation testing, and provide a finite and restricted thermal nerve lesion (20). RTR produces some sensory loss in the affected distribution, which is usually well tolerated. It does not affect facial nerve function, and therefore facial muscle paresis is not a concern. Pain relief is generally immediate, complication rates and side effects are minimal (the latter usually well tolerated), and patient satisfaction is high (26).

The specific aims of this study were: (A) to evaluate the effectiveness of our management algorithm for TN, (B) to compare medical and surgical treatment outcomes, and (C) to evaluate RTR in patients who did not benefit from or could not tolerate medical management.

Methods

Patient Management Protocol

Patients who presented to the MGH Craniofacial Pain Center between 1991–1996, with a complaint of facial pain, were considered for participation in this study. They were evaluated with a comprehensive interview, history and physical examination. Physical examination of the head and neck consisted of examination of the cranial nerves, with special attention to the neurosensory examination of the trigeminal nerve. Patients with the following five findings were diagnosed with TN: (A) paroxysmal, lacinating, electric-like pain, (B) tactile trigger areas, (C) unilateral symptoms, (D) restricted to the distribution of the trigeminal nerve, and (E) no neurosensory deficit. These patients were entered into our management algorithm (Fig. 1).

All patients with this diagnosis were evaluated by magnetic resonance imaging (MRI) of the brain and brainstem, with special attention to the posterior cranial fossa and trigeminal system, for evidence of tumor, vascular abnormality or demyelination (Fig. 1A). Patients with a clinical diagnosis of TN and a normal MRI were started

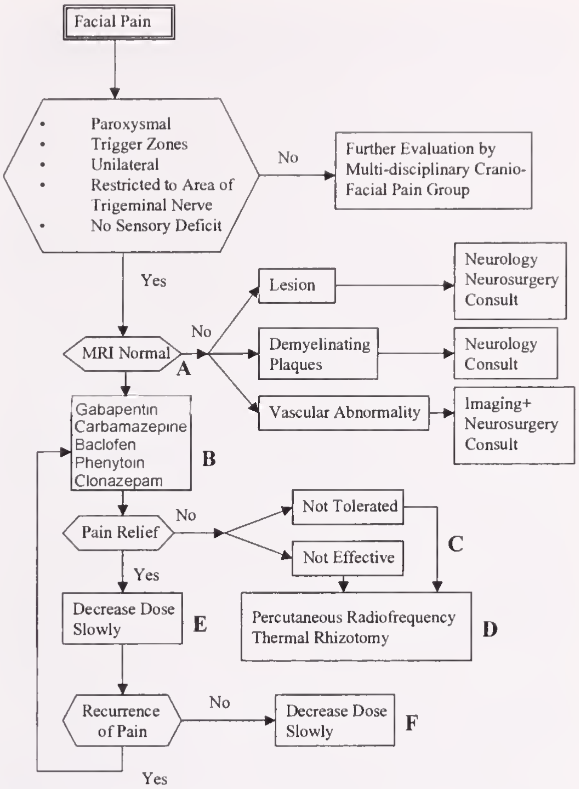
Facial Pain
Paroxysmal
Trigger Zones
Unilateral
Restricted to Area of Trigeminal Nerve
No Sensory Deficit
No
Further Evaluation by Multi-disciplinary Cranio-Facial Pain Group
Yes
Lesion
Neurology Neurosurgery Consult
No
MRI Normal
A
Demyelinating Plaques
Neurology Consult
Vascular Abnormality
Imaging+ Neurosurgery Consult
Gabapentin
Carbamazepine
Baclofen
Phenytoin
Clonazepam
B
Pain Relief
No
Not Tolerated
Not Effective
C
Yes
Decrease Dose Slowly
E
Percutaneous Radiofrequency Thermal Rhizotomy
D
Recurrence of Pain
No
Decrease Dose Slowly
F
Yes

Fig. 1. Algorithm for the management of trigeminal neuralgia (TN).

- **A.** MRIs of the brain, brainstem, and base of the skull are obtained. Further evaluations and studies are only performed when physical examination or MRI findings are abnormal.
- **B.** Medication is titrated progressively until pain is relieved or adverse effect(s) occur.
  1. Carbamazepine 300–1200 mg per day or
  2. Baclofen 20–80 mg per day or
  3. Gabapentin 300–1200 mg per day or
  4. Phenytoin 300–1200 mg per day or
  5. Carbamazepine + Baclofen or
  6. Gabapentin + Baclofen
  7. Clonazepam 0.5–1.0 mg per day is often added to the above regimens.
- **C.** Drug allergy or idiosyncratic reaction, laboratory abnormalities (CBC, Liver function tests, drug levels), significant side effects, patient preference.
- **D.** Prior to radiofrequency thermal rhizotomy, local anesthetic blocks are performed in some patients as part of a further evaluation of individual nerve divisions and to permit the patient to experience the feeling of altered sensation.
- **E.** Dosages of medications are decreased slowly in a stepwise fashion depending on the prior regimen providing pain relief. After the patient has been pain free for 4–6 weeks, medication can be gradually tapered and eliminated.
- **F.** Further decrease in dosage of medication is predicated on the patient's pain history. Many patients are maintained on pharmacologic therapy.

on pharmacologic therapy (Fig. 1B). Those patients who did not conform to the clinical diagnosis of TN, or who had abnormal MRI findings were further evaluated, and appropriate consultations and further diagnostic studies were ordered. These patients were not included in this study.

Patients were prescribed pharmacologic regimens based upon past drug history and responsiveness to specific pharmacologic agents. Pharmacologic therapy was continued and adjusted based upon pain relief and patient tolerance. If pharmacologic therapy was effective in providing adequate pain relief, it was continued and the patients were monitored closely for 4–6 weeks. The dosage(s) of medications were slowly tapered in a stepwise fashion (one medication at a time over 2–4 weeks), monitoring for return of pain (Fig. 1E). With a decreasing dose of medications, if there was a recurrence of pain, the prior drug regimen was re-instituted. Patients who remained pain free were tapered off all medications. However, some patients were maintained on low-dose, prophylactic pharmacologic programs because of intermittent spontaneous or triggered bouts of pain (Fig 1F). Patients for whom pharmacologic therapy was either not effective in providing adequate pain relief and/or was not well tolerated, were considered for surgical treatment with RTR (Fig. 1C); this was 39% of the total study group.

All patients considered appropriate candidates for RTR were interviewed and counseled. The procedure was thoroughly explained and the risks and benefits outlined and discussed. The potential complications and side effects were described and explained in terms that the patients could fully understand. All patients were given a written description of the procedure to facilitate their review of it. Additionally, patients were advised of the surgical alternatives to RTR, namely glycerol rhizolysis, percutaneous balloon compression of the trigeminal ganglion, and posterior fossa exploration / microvascular decompression. The risks and benefits of these other procedures, and similarities and differences to RTR, were explained and discussed. Any patient who wished further surgical consultation was promptly referred to the appropriate individuals at our institution. Patients who finally consented to undergo RTR were included in this study.

RTR Protocol

RTR is a surgical procedure on the trigeminal (Gasserian) ganglion, performed by a percutaneous approach with local anesthesia, intravenous sedation and intermittent general anesthesia administered by a senior neuroanesthesiologist. The surgical approach utilizes specific anatomic landmarks and radiologic guidance. In 1974, Cosman and Cosman (27) described the history of the development of the modern radiofrequency generator, many basic fundamentals of utilizing the machine, and the various technical parameters, critical for effective treatment.

The modern radiofrequency generator has a built-in impedance monitor, a stimulator, temperature monitor, and a display of voltage and milliamperage. It has a complex timing device that automatically turns off radiofrequency heating at a desired time interval. Cosman states that the radiofrequency lesion electrode is minimally invasive with an electrical shaft that can communicate impedance, stimulation, recording temperature and lesion parameters that go back to the operator for exquisite target identification and lesion control (27). The voltage meter essentially records electrical energy. The milliamperage is the delivered power or current flowing through the tissue. At a given temperature, an inappropriately increase in the milliamperage may reflect dissipating energy secondary to breaks in the circuitry. The impedance ohmmeter measures the resistance to flow of energy. Resistance of 250–260 ohms is seen in nerve root and rootlets, and may drop to 190–200 ohms when in spinal fluid, while an increase of resistance to 400 ohms may imply bone. This auxiliary electronic aid is certainly most helpful for the improvement of lesion making as well as safety of the patient. Finally, the stimulator is most important in localization for final lesion making.

RTR is performed in the Ambulatory Surgical Suite, with the patient in the supine position on a mobile X-ray table. All patients are likely to be apprehensive, and reviewing each step of the surgical procedure at this time is helpful and important. The head and shoulders are placed on a headboard which extends the head over the end of the X-ray table, allowing for an easy sweep of the C-Arm videofluoroscopy unit. The head may then be extended over a foam sponge so that the view of the foramen ovale is obtained. Extension may be up to 20 degrees and rotation of 15–20 degrees away from the side of the pain (28), for optimal visualization of the foramen ovale. The foramen ovale is seen through the pterygomandibular and infratemporal space as an oval structure at the top of the petrous pyramid. Once the foramen is adequately visualized, the image is stored in the fluoroscopy computer and can be reproduced at any point during the procedure.

Following satisfactory imaging of the foramen ovale, the face is surgically prepared and local anesthesia is infiltrated into the skin and subcutaneous tissues of the ipsilateral cheek. A large bore (#15) needle is then placed through the skin in this area to allow for easier passage of the cannula and its stilette. The surgical instruments and electrode enter the skin 2.5 – 3.0 cm lateral to, and 0.5 – 1.0 cm below, the labial commissure (Fig. 2) (20, 21, 29). The direction of the instrument is determined by two planes: a lateral plane at a point one-third of the distance from the external auditory meatus to the lateral canthus of the eye, and a medial plane directed from the puncture site to the medial aspect of the pupil. Intersection of these planes indentifies the site of the foramen ovale (Fig. 2).

Once the foramen has clearly been identified, a 19-gauge insulated cannula with a sharp stilette is introduced through the puncture site. The neuroanesthesiologist then anesthetizes the patient with an intravenous agent (propofol) which is rapid in onset and ultra-short in duration, to allow the surgeon to proceed with advancing the cannula. The cannula is directed slightly downward and laterally for approximately 2.5 cm. This trajectory is then changed back into Hartel's projection (30) to avoid entrance into the oral cavity. The cannula may be in the perioral tissues, and a quick look will assure the surgeon that the cannula has not penetrated the oral cavity. The cannula and stilette are now directed toward the medial portion of the foramen ovale in the AP projection. The suggested trajectory through the foramen ovale is determined by the division(s) involved and to be lesioned (Fig. 3) (20, 21). The initial trajectory should aim for a point at the junction of the clivus and petral-clinoid ligament and never approach the floor of the sella. From that point to the petrous pyramid, a line is then divided into three points, the uppermost being the first division trajectory, approximately 50% from the petrous pyramid to the junction of the petral-clinoid ligament and clivus for the second division, and just above the petrous pyramid at the junction of the clivus for the third division. The cannula and stilette are advanced to a point 1 mm in front of the clivus. The stilette is now removed, and in most instances there is free-flow cerebrospinal fluid; however, this is not always mandatory for a successful procedure. Often just rotating the hub of the cannula or placing the patient in Trendelenburg position may allow fluid to egress.

Once a satisfactory position has been obtained, the stilette is removed and replaced with a straight or curved "Tew" electrode (21). The patient is now fully awakened, and once again, the surgeon reviews the previously prepared steps with regard to the patient assisting in localizing the square-wave stimulus. The square-wave (pulsed at 50 cycles per second for 1 millisecond and 0.1 –0.28 volts) will allow the patient to identify the location of the stimulus on the face. If it requires more than 0.25 –0.28 volts, the electrode will have to be readjusted. Initial temperature on the generator should be approximately 37°C. The impedance ohmmeter should read approximately 100 – 260 ohms.

The patient is instructed to signal, the moment that he or she feels a nonpainful stimulus (square-wave pulse). The third division is often felt in the lower lip, teeth and chin, the side of the

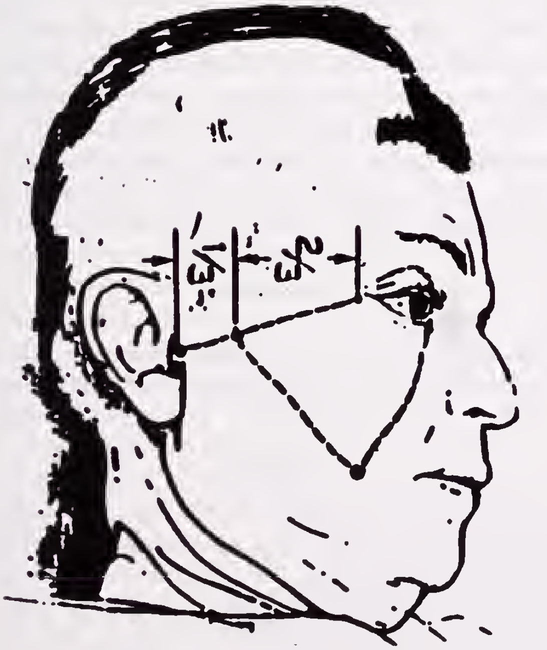

Fig. 2. Skin gridlines for penetration of the foramen ovale and Gasserian ganglion.

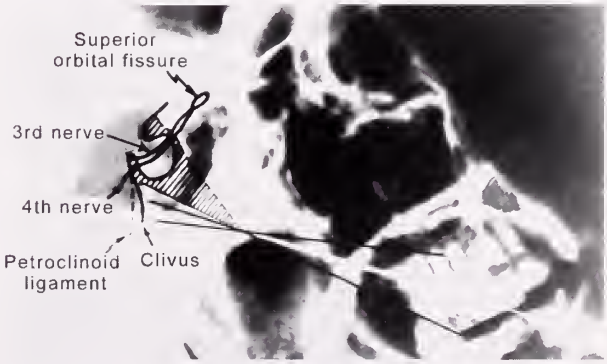

Fig. 3. Lateral projection for electrode placement into appropriate divisions of the trigeminal nerve.

TABLE 2
Characteristics of Patients

	Present Study	Historic Control**
Average Age	61.5 years (range=41 – 95)	65 years
Sex	69% female	62% female
Side of the face	58% right	60% right
Division involved		
V-1	0	1%
V-2	13%	16%
V-3	38%	15%
V-1, V-2	8%	15%
V-2, V-3	33%	40%
V-1, V-2, V-3	4%	13%

** Tew JM, van Loveren H. In: Schmidek HH, Sweet WH, editors. Operative neurosurgical techniques: Indications, methods and results, Vol. 2. Philadelphia (PA): W.B. Saunders Co.; 1988. (Reference 57)

years. Females, the right side of the face, and the third division were most commonly affected. There were no patients with isolated first division involvement, and only 8% had first division involvement at all.

Postoperatively, we evaluated patients for early results (immediately postoperative to 6 months) and long-term results (>6 months to 68 months). The grading scale, "description of early results" described in 1995 by Tew and Taha (Table 1) (21) was used for evaluation of outcomes. Patients were also evaluated for complications and side effects of the procedure. Our complications were classified and compared to published combined series data (Table 3) (21).

TABLE 3
Complications

	Present Study	Historic Control**
Masticatory muscle weakness	28.8%	23%
Dysesthesia	8%	20%
Anesthesia dolorosa	2%	1%
Corneal analgesia	3%	7%
Keratitis	0.8%	2%
Aseptic (chemical) meningitis	0.8%	2%
Bacterial meningitis	0	0.2%
Carotid-cavernous fistula	0	0.1%
Intracranial hemorrhage	0	0
Diplopia	0	1.2%
Other cranial nerve deficits	0	0
Death	0	0

** Tew JM, Taha JM. Percutaneous rhizotomy in the treatment of intractable facial pain (trigeminal, glossopharyngeal and vagal). In: Schmidek HH, Sweet WH, editors. Operative neurosurgical techniques, Philadelphia (PA): WB Saunders; 1995. (Reference 21)

Early pain relief (immediately postoperative to 6 months), classified as excellent or good (successful), was obtained in 224/258 patients (87%). The remaining 34 patients experienced only fair or poor pain relief, which was considered to be an unsuccessful outcome. At long-term follow-up, tic pain recurred in 68 patients (26%). Of this group of patients, 31 (12%) required re-operation and 37 (14%) were managed with medical therapy alone (Table 4). Long-term excellent or good (successful) pain relief ultimately was achieved in 214/258 patients (83%).

There was no mortality or major morbidity. Two patients developed postoperative symptoms that were considered consistent with aseptic (chemical) meningitis; they were hospitalized and appropriately evaluated and treated. Blood cultures for both patients were negative and neither patient became septic. The cerebrospinal fluid analysis was normal. Both patients' symptoms resolved uneventfully, and they were discharged from the hospital in 2–3 days.

In our study, 92% of the patients who underwent RTR had early complete pain relief. Overall, late recurrence rate was 26%. Dysesthesia developed in 21 patients (8%); 8 patients (3%) had dysesthesia alone (medically managed) and 13 patients (5%) had dysesthesia with recurrence of tic pain (medically and/or surgically managed). "Anesthesia/analgesia dolorosa" developed in 5 patients (2%). Corneal analgesia developed in 8 patients (3%), with 2 of these patients developing transient keratitis that required ophthalmologic evaluation and treatment. No patient developed ocular muscle paresis or visual loss (see Table 5). Approximately 29% of the patients developed transient ipsilateral masticatory muscle weakness, but no patient developed motor branch involvement that resulted in masticatory muscle palsy or permanent functional impairment. No other cranial nerve deficits were encountered.

Discussion

Both dental and medical specialists are involved with the evaluation and treatment of

TABLE 4
Results

Early pain relief (0–6 months)	224 / 258 (87%)
Unsuccessful (0–6 months)	34 / 258 (13%)
Recurrences requiring re-operation	31 / 258 (12%)
Recurrences not requiring re-operation	37 / 258 (14%)
Long-term pain relief (> 6 months)	214 / 258 (83%)

Mean follow-up = 38 months (range: 12–80 months) temple or even the ear. The second division stimulus may include the upper lip, teeth, the side of the nose and the middle of the cheek. Stimulation in the first division can give you a reference to the eye, the eyebrow or the forehead. When the patient has identified the area of stimulation and the voltage required is below 0.2 volts, the position is reconfirmed with a mild heating stimulus. The initial response will be between 40–48°C, characteristic for patients undergoing an initial radiofrequency procedure. If there is no satisfactory response or the patient does not experience tingling or heat, the electrode position must be changed. We have found that the curved "Tew" electrode with a coiled spring at its tip may be useful. In the lateral projection, the tip of the electrode is never more than 2–3 mm behind the clival profile. The patient will often tell you that the place of your stimulus is where he feels his pain. The position of the electrode is constantly checked by fluoroscopy to prevent inadvertent moving during stimulation and/or heating.

Once this satisfactory location has been achieved, the neuroanesthesiologist renders the patient unconscious for lesioning. If the threshold for heat was 48°C, the first lesion is made at 60°C for 60 seconds. During the heating, a facial flush has often been observed; it has been described by others as a secondary release of vasodilatory neuropeptides such as substance P (28). This facial flushing confirms the position of the electrode as well as localizing the division that is undergoing neuronal changes secondary to radiofrequency heat. Modern radiofrequency lesion generators are equipped with a timer that turns off the heating element, making it almost foolproof for the surgeon.

The patient is now allowed to awaken completely, following which stimulation by pinprick across the midline may be followed by an aversive response, suggesting an early lesion as one passes the midline to the normal side. If there is no appreciable analgesia or change in sensation, the procedure and lesions are repeated by increasing the temperature by 5–8°C in an incremental way for 60 seconds, until a satisfactory and desired degree of analgesia has been achieved. Sensory testing should be carried out when the patient has fully recovered from intravenous sedation; often, in elderly patients, this may be a problem. All patients are always tested for the corneal sensation, and if there is any change whatsoever, the procedure is promptly discontinued. We have tried to have the patient assist in determining when the endpoint has been reached. We asked those patients who have recurrent trigeminal neuralgia if the degree of numbness is tolerable or whether they wish it to be more numb. In an unanesthetized and responsive patient, when heating evokes little or no reaction, the presence of a thermal lesion can be assured at the completion of the procedure. After the patients have adequately recovered, they are usually discharged home with a companion later that day. If any complications are encountered during or after the procedure, the patient is admitted to the hospital for further observation.

All patients were followed in person, or by telephone interview, at one week, one month, six months, and then yearly. Patients were questioned and examined for facial hypesthesia/hypalgesia, dysesthesia, side effects and complications. All patients were asked to give a satisfaction rating for the management of their pain after RTR, using the published "description of early results" criteria: excellent, good, fair, poor, failure (Table 1) (21). Excellent or good results are considered successful, with no tic pain and no, or only minor dysesthesia. Fair and poor results are considered unsuccessful, with some tic pain and moderate to major dysesthesia. Patients with a recurrence of pain were re-examined and re-entered into the management algorithm on their prior pharmacologic regimen. Patients with recurrence of pain that did not respond to additional pharmacologic therapy were considered for re-operation.

Results

Between 1992 and 1996, a total of 662 patients were seen in the clinic, of whom 258 (39%) were ultimately diagnosed with TN and underwent surgical treatment with RTR. These patients were followed prospectively for a period of 12 to 80 months, the mean follow-up time being 38 months.

The patients were characterized by age, sex, side of the face and division(s) involved. Comparison was made between this patient group and previously published historical controls (Table 2). The average age of patients in this study was 61

TABLE 1
Description of Results

Result	Description
Excellent	No tic pain, dysesthesia, or troublesome paresthesia
Good	No tic pain, minor dysesthesia / paresthesia
Fair	No tic pain, moderate dysesthesia / paresthesia
Poor	Tic pain, major dysesthesia / paresthesia
Failure	Immediate

TABLE 5

Comparison of Different Procedures in the Treatment of Trigeminal Neuralgia

(Values represent per cent of the number of patients studied)

Technique	Immediate relief	Recurrence	Dysesthesia	Anesthesia dolorosa	Weakness	Morbidity	Mortality
Radiofrequency Rhizotomy (Present Study)	92	26	8.4	1.8	29	1.8	0
Radiofrequency Rhizotomy (46)	98	23	10	1.5	24	1.2	0
Glycerol Rhizotomy (46)	90	54	55	1.8	1.8	1.0	0
Balloon Compression (46)	93	22	5	0.1	66	1.7	0
MVD (46)	95	17	0.4	0.1	0.1	10	0.6

MVD = microvascular decompression.
(46) = see reference 46.

patients with craniofacial pain disorders. It has been shown that many patients with these types of problems can go undiagnosed or misdiagnosed, with multiple diagnostic and therapeutic interventions prior to being given the correct diagnosis (8, 32, 33). While the diagnostic criteria for TN are quite specific, not all patients give a "classic" history, and often the physical examination gives information that can be confused with other neurogenic and non-neurogenic pain disorders of the head and neck. To avoid these problems and provide appropriate disease-specific treatment that is evidence-based and effective, an algorithm for the diagnosis and management of TN developed by our clinical group, is presented in this study. This study uses the algorithm to correctly diagnose TN, which is a prerequisite for a successful outcome with RTR.

In the treatment algorithm used for this study, an MRI of the brain, brainstem and cranial base was performed in those patients in whom the clinical diagnosis of TN was made. Reviews of TN by Sweet and others have shown that pathology in any of these regions can produce signs and symptoms that could be confused with primary TN. Multiple sclerosis (MS) (35–37), Chiari malformation (38), pontine hemorrhages (39), midbrain lesions (40), cerebellopontine angle tumors (41), other tumors (42), and most notably, vascular compression (43–45), have all been implicated in causing TN. While the purpose of this study was not to document pathology causing secondary TN, numerous patients in our study were found to have pathology thought to be the cause of their TN; meningiomas, schwannomas, MS plaques, ectatic basilar artery, pituitary tumor and metastatic disease. With this algorithm, these patients were able to be correctly diagnosed and were referred for the most appropriate treatment.

In the present study, 39% of the patients underwent surgical treatment with RTR, while the majority were managed with pharmacologic therapy. This is quite different from other studies, in which 60–75% or more had surgical treatment (14, 21, 46). Regardless of the risks of drug therapy, many patients will benefit from aggressive pharmacologic management with newer agents which have less debilitating and potentially dangerous side effects. Multiple drug regimens, given as initial treatment, may also provide better pain control, and even remission. While the results of this study show that RTR is very effective and is associated with only limited side effects, it must be noted that surgical intervention may cause significant debility from dysesthesia, keratitis and anesthesia dolorosa. Medical therapy prior to surgical consideration is necessary and can be effective in many patients.

Overall comparison of our results with those published (see Table 5) indicates that our results were slightly less successful. The reason for this difference is possibly related to patient selection based on clinical considerations and indications for RTR. The relevant issues of the procedure and the decision-making process were throughly discussed with each person and his/her family individually. Nonetheless, pain control is the ultimate goal of RTR, a selective neuroablative procedure which can be performed in a differentially graded fashion. Thus pain relief may be achieved and the more troublesome side effects avoided or minimized.

This conceptual approach to performing RTR may have had an impact on the initial success rate.

Our recurrence rate (26%) was similar to that of other series, as was our rate of anesthesia dolorosa (Table 5). Our rate of dysesthesia was significantly less than that of other series (44, 46, 47). Pain recurrence following a successful RTR may not be related to the technique of the procedure, but is most likely a property of the still unknown disease process. Once a successful thermal lesion is made, the long-term anatomic, histologic and neurophysiologic changes that occur are not known. This probably has some clinical relevance to long-term pain relief and recurrence rates, along with possibly altering the pathophysiologic process that is responsible for producing TN.

Anesthesia dolorosa is an infrequent, but unfortunate complication of RTR as well as other neuroablative procedures. The mechanism for loss of sensation with continued pain is presently not fully understood. It is thought that this represents a central process of abnormal modulation and processing of afferent signals and is not solely the result of peripheral nerve damage (2). Prevention of this problem from occurring at all following RTR probably lies in careful patient selection for RTR, and not in the surgical technique.

It has been shown that the level of sensory loss was correlated to the rate of dysesthesia and the length of time the patient was pain free (47). Mild hypalgesia was correlated with less dysesthesia, but less time pain free, whereas, analgesia was correlated with more dysesthesia, but greater time pain free. This balance between pain relief and the probability of producing dysesthesia following RTR, is difficult to predict and difficult to control. We postulate that our rate of dysesthesia is lower than other series due to careful patient evaluation, careful selection of patients for RTR, and most important, the production of small, precise lesions producing hypalgesia and not analgesia or anesthesia.

Our rates of additional complications (muscle weakness, corneal analgesia, keratitis and aseptic meningitis) are consistent with other series. These problems, while not insignificant, do not produce major morbidity or functional deficits. Masticatory muscle weakness progressively improves spontaneously and can be additionally helped with physical therapy and passive mandibular motion exercises. Corneal analgesia is also usually transient and can be managed successfully with topical preparations and artificial tears. Our one case of keratitis was promptly diagnosed and the patient referred to an ophthalmologist; treatment prevented corneal scarring or loss of visual acuity. Aseptic (chemical) meningitis in some patients may have been due to an inflammatory reaction to the intracranial manipulation. Our two patients with postoperative symptoms consistent with meningitis were referred for prompt medical evaluation. They were found not to have infectious meningitis, and were successfully managed on an outpatient basis without complications. More serious complications, as indicated in Table 3, did not occur in our study group.

When considering surgical treatment for TN, there are several procedures that are commonly utilized. These were recently compared with respect to efficacy, side effects and complications (47). Of the percutaneous procedures, RTR has the best overall, long-term outcome data. The initial pain relief is equal to or better than that gained from other procedures, the recurrence rate is lower, and the side effects and complications are less frequent and less morbid. RTR allows for pre-lesion testing for localization in order to produce a lesion in only the division(s) involved. RTR also affords the ability to clinically test after a lesion(s), in order to grade the level of hypalgesia/paresthesia, and possibly avoid side effects, while still providing pain relief.

Glycerol rhizolysis is not division specific, and has a very high recurrence rate (approximately 50%) and an equally high incidence of dysesthesia. Balloon compression of the ganglion is also not division specific, can produce significant bradycardia and hypotension during the procedure, has a very high incidence of masticatory motor dysfunction and other cranial nerve abnormalities.

The long-term follow-up data after microvascular decompression (MVD) indicates that it is very effective, and typically does not produce a sensory deficit. However, it has several significant disadvantages when compared to RTR. Those who perform MVD routinely argue that the procedure is safe and effective (44, 47). Yet MVD requires a craniotomy with retraction of the cerebellum and brainstem. Cerebellar dysfunction, hearing loss and facial palsy may result. While these complications are infrequent, the risk may be viewed by the patient as inappropriate or unacceptable.

Stereotactic radiosurgery using the gamma knife has been reported to have a role in the surgical treatment of TN (48, 49). Recently, a multi-institutional study and a follow-up single institution study have found gamma knife radiosurgery to be safe, effective, non-invasive and to have very minimal side effects (50, 51). While these results are encouraging, there are only very short-term follow-up data available. Numerous additional questions regarding safety and justification remain (52).

Other open surgical procedures involving the root entry zone and the trigeminal brainstem nuclear complex are still being performed, with limited success and the potential for significant complications (53–55). The overall success rate for treating TN is approximately 50% and the complications are often significant and catastrophic; limb and leg ataxia, weakness, sensory loss and death (55, 56).

Those who treat TN, whether surgeon or not, must know all the benefits, risks and complications of all the surgical procedures used to treat this problem. Physicians need to take whatever time is necessary to counsel patients and family about these treatments and to be assured that they fully understand all their options before undergoing any treatment regimen, regardless of the physicians' personal bias. With any surgical procedure there are potential risks and complications, but under no circumstance should the potential cure be worse than the disease.

Conclusion

The management algorithm presented in this study is an effective way to evaluate, diagnose and treat patients with TN. Surgical treatment with RTR is a safe and effective way to manage patients with TN in whom pharmacologic therapy is either ineffective or not tolerated. The side effects of RTR are low and are well tolerated. We believe that RTR should be the procedure of choice for initial surgical management of TN.

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Frameless Stereotaxy of the Brain

James McInerney, M.D., and David W. Roberts, M.D.

Abstract

Today's neurosurgical journals are replete with advertisements for systems designed to provide image guidance during surgery. These so-called "frameless" stereotactic systems provide the surgeon with navigational information, relating the location of instruments in the operative field to preoperative imaging data. Such information minimizes invasiveness by more accurately selecting the best trajectory to the lesion, ensures more precise identification of normal structures, and guides complete removal of a lesion. To achieve these goals, all of these systems utilize the stereotactic principle of co-registration of the patient with an imaging study.

This review will trace the development of image-guided surgery from its origins in frame-based stereotaxy to its current use as a surgical navigation methodology. A review of the more prevalent techniques and available systems will be presented, along with examples of specific applications of surgical navigation. Finally, some of the future directions of frameless stereotaxy will be discussed.

Key Words: Computer-assisted surgery, image-guided surgery, stereotaxy.

Historical Background

Early stereotactic systems used a frame to satisfy the need for accurate co-registration and probe guidance. By fixing a frame to the head, Horsley and Clarke (1) were able to define a coordinate system in space that effectively included the intracranial contents. This defined space could then be related to a known atlas of the brain, and a probe could be directed to a specific site within the defined space. This proved to be a useful laboratory technique, but did not take into account normal anatomic variation. It was not immediately extended to clinical practice.

Co-registration of frame-defined space with an individual imaging study followed. With the frame in place during the radiologic exam, imaged anatomic structure was located in the frame's coordinate system. This technique was limited by the information discernible on plain radiographs, pneumoencephalography, positive contrast encephalography and, later, angiography, so reference to co-registered atlases was still necessary. The location of structures not appearing on the image, such as the ventrolateral nucleus of the thalamus, could be inferred by their known relationships to structures that were visible, such as the anterior and posterior commissures. The advent of computerized tomography significantly improved the anatomic localization of specific structures and their interrelationships. Calculations to direct a probe to a specific site seen on the study were simplified, and more intracranial structures were directly visualized. Not surprisingly, application of the methodology to biopsy tumors became widely popular. Atlas relationships were still necessary for the location of less well visualized structures, such as the nuclei of the thalamus, but the accuracy and ease of the calculations determining these relationships in the defined coordinate system were considerably improved. With the introduction of magnetic resonance imaging and its still greater resolution, the need for atlas relationships was further reduced:

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Dr. David W. Roberts is a member of the Scientific Advisory Board of Elekta AB, Stockholm, Sweden. The U.S. patent (no. 4,722,056) describing a stereotactic operating microscope, assigned to the Trustees of Dartmouth College, has been licensed to Elekta AB.

many conventionally targeted intracranial structures are now directly visible on the imaging study.

With all of this imaging information available, it became clear that the application of stereotactic technique held far more promise than had previously been realized. Adequate mapping data was available to guide the surgeon directly to a lesion or structure. The location of normal structures could be identified with greater accuracy, enhancing the ability of the surgeon to avoid injury to these structures. Finally, by co-registering the surgical field and instruments with a fully three-dimensional imaging study, the exact location of instruments within the field could be determined, which in turn allowed greater confidence in the extent of a lesion's resection.

Development of Frameless Stereotactic Systems

The stereotactic frame had been essential to the conceptualization of stereotactic technique because it was the tool through which co-registration and instrument guidance were achieved. The stereotactic frame is limiting, however, in a number of respects. It generally provides targeting of only a single point rather than orientation to three-dimensional anatomy. Further, it functions primarily to direct a probe to a preselected target, not to find the location of an independently positioned instrument on an image. In addition, the frame itself is a physical constraint during surgery.

The advent of accessible personal computers and affordable workstations provided the means to address some of these limitations. These processors enabled a variety of digitizing technologies to be brought into the operating room – technologies which could both define surgical coordinate space and locate points within that space. The computational ability of even the earliest personal computers could also perform the necessary calculations to co-register the surgical field and an imaging study. Lastly, these workstations could drive the graphics displays to make co-registered information useful to the surgeon. In accomplishing these three tasks of digitization within a coordinate space, co-registration of multiple coordinate spaces, and end-effector information, the operating room computer carried out all the tasks of the frame and itself became a stereotactic instrument.

The earliest prototype systems served primarily to demonstrate a concept, although from the onset the powerful utility of their guidance was appreciated. While numerous investigative groups developed systems of their own and a diversity of components and methodologies developed, the principles underlying the concept of frameless stereotaxy remained unchanged. Finally, the involvement of industry working in collaboration with early investigators brought refinement in the instrumentation and techniques, enabling widespread dissemination of the technology.

Specifics of Image-Guided Systems

Digitizers

Digitizers, whether mechanical or nonmechanical, are computerized systems that provide coordinate addresses for any accessible point within their working volumes. It is the means by which they accomplish this that distinguishes between the many types of digitizers.

Sonic Digitizers

When the Dartmouth program first explored types of digitizers that would free a stereotactic system from mechanical linkage to the surgical field, a decision was reached to implement a frameless system using a sonic digitizer. It was a well-established and affordable means to demonstrate a concept. Today, the cost and availability of other methods have made them competitive alternatives.

Acoustic range finders determine the distance between a microphone and a small spark gap that emits a broad-bandwidth click by measuring the time of flight of that acoustic impulse. Sensitive to air temperature, humidity and turbulence, this technique may appear difficult, but accuracies in the range of 0.15% over a 100-cm slant-range are realistic in commercially available systems, such as that of Science Accessories Corporation (Stratford, CT). Using an array of at least three microphones, the location of a spark gap in three-dimensional space can be uniquely determined. Through refinement of software algorithms and other modifications (such as a pilot calibration pole consisting of a spark gap and microphone separated by a known distance that thereby obviates the need to directly measure temperature), the accuracy of these systems can be further improved and made clinically useful. They do require line-of-sight between emitter and receivers.

Our first stereotactic operating microscope system used such a digitizer to track the position and orientation of a microscope to which an array of three spark gaps had been attached (2–7). Early prototypes worked with an array of three or four microphones initially on the ceiling and subsequently on an adjustable light track over the surgical field; eventually, the microphone array was attached to the operating room table itself. This last modification was greatly appreciated by the surgical staff, as it allowed the table to be moved without re-registration, a practice eventually incorporated into most frameless systems today, regardless of the digitizing technology employed.

Each time the microscope was moved, the spark gaps fired and the position was re-determined. The relationship of this new position to the imaging studies was then calculated and that information made available to the surgeon in a number of ways, as discussed later. While the earliest system obtained initial registration of the microscope and the surgical field by focusing the microscope on each of three scalp fiducial marks, this registration step was later facilitated by simply positioning a hand-held single spark gap at these fiducials sequentially.

Sonic digitizers have been incorporated into frameless systems by at least three other groups as well. Barnett, Kormos and colleagues (8–12) developed a "sonic digitizing wand" system using this technology interfaced initially to a Sun SparcStation I (Sun Microsystems, Mountain View, CA) and more recently to a more powerful Picker ViStar Medical Imaging Supercomputer (Picker International, Highland Heights, OH). Using hand-held instruments such as a bipolar cautery to which two spark gaps have been attached and a table-mounted microphone array, they have reported a mean linear error in localization of 66 targets in 22 patients of 3.1 mm ± 1.5 mm (SD), with 3 mm computer tomography (CT) slice thickness or 2 mm voxel magnetic resonance imaging (MRI) volume acquisition (11).

Reinhardt and colleagues (13–15) have independently developed a sonic-based system for the localization of hand-held instruments in the surgical field. In a later version of their system using a Science Accessories Corp. GP8-3D digitizer and an IBM-compatible personal computer, the microphones are placed on the instruments and the spark gap emitters on the distant array. They have reported digitizer accuracy in the laboratory of 0.897 mm ± 0.635 mm SD (15).

Bucholz and Smith (16) have reported an additional laboratory and preliminary clinical experience with a sonic digitizer. In the controlled, non-clinical setting, they achieved system performance similar to that of Reinhardt's, although their system was less reliable in the nine operative cases reported.

Articulated Arms

Articulated mechanical arms allow localization within the surgical field through knowledge of the fixed length of each link and the angle at each joint. The latter can be measured by either potentiometers or optical encoders. With this information, it is possible to know the location of the tip of such an arm with respect to its base. After an initial registration step, the tip of the arm in the surgical field can be related to preoperative imaging studies. Watanabe and colleagues first reported this (17–21), and numerous other implementations, including those of Mosges and Schlondorff (22–24), Adams (25), Leggett (26), Guthrie (27–29), Maciunas (30–32), Goerss (33), Koivukangas (34), and Zinreich (35), have demonstrated the practicality of such a technique. The Mark II arm of the Vanderbilt group illustrates the kind of accuracy that can be achieved with an arm of this type. Measurement errors for known distances in the laboratory have been on the order of 0.14 mm ± 0.139 mm (SD); the average error in clinical use has been 2.35 mm ± 1.18 mm, and this subsequently has been improved even further (32). Such arms are without line-of-sight constraints, and are relatively easy to use and generally reliable in differing environments. They vary in size, weight and balance, but all involve the potential encumbrance of an additional mechanical instrument in the field.

Closely related to these passive, articulated localizing arms are robotic instruments in which actuators may actively drive the end effector to a selected point and orientation (Fig. 1). Investigations to date, including the pioneering work of Young (36) and Kwoh (37), Glauser and Fankhauser (38, 39), Drake (40–42), and Benabid (43), have demonstrated the feasibility of such an approach. Automated delivery of invasive instrumentation has not yet been widely embraced. Such acceptance awaits further development of the technology for reliability and safety. Robotic instrumentation may be used to position operating microscopes, as in the implementations of the SurgiScope (Elekta AB, Stockholm, Sweden) and the MKM (Zeiss, Oberkochen, Germany) systems, as well as that of Giorgi (44). An extension of this methodology to radiosurgery is under development at Stanford University, where a lightweight linear accelerator is being positioned by a robotic manipulator (45, 46).

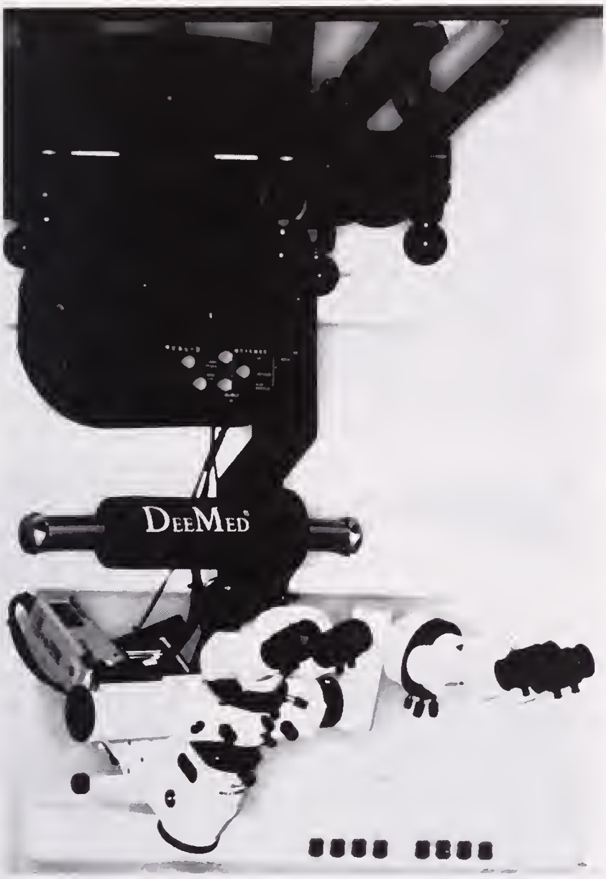

Fig. 1. This ceiling-mounted robotic operating microscope holder (SurgiScope, Elekta AB, Stockholm, Sweden and DeeMed, Grenoble, France) is capable of both monitoring the position of the microscope's optical focal point and robotically positioning the microscope at a target selected on an imaging study.

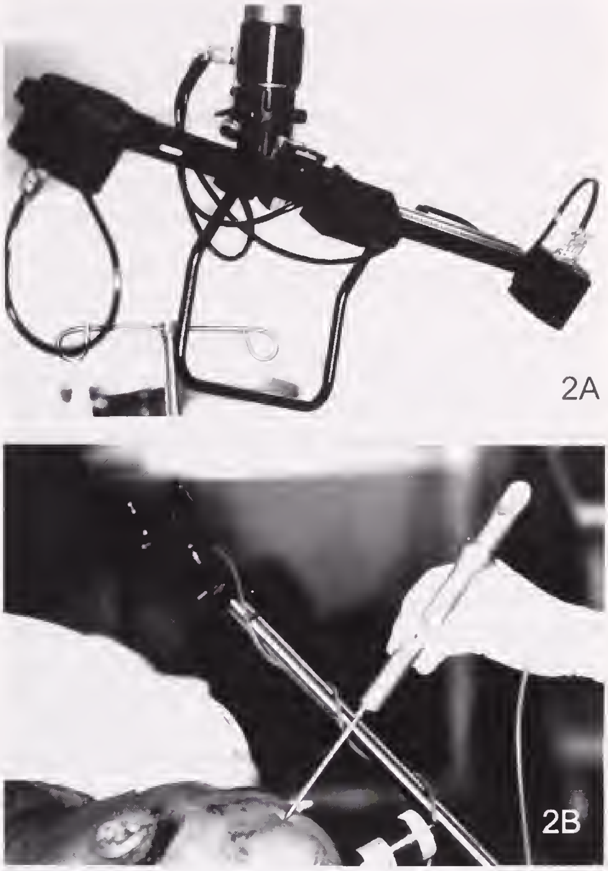

Fig. 2. **(A)** This optical digitizer by Pixsys, Inc. (Boulder, CO), consists of three cameras on an overhead bar that can track LEDs attached to any instrument in their field of view. LED arrays attached to hand-held instruments or to the operating microscope enable them to be tracked. **(B)** An LED array attached to the head clamp enables registration to be maintained when the operating table is moved.

Optical Digitizers

A variety of digitizing methodologies based upon optical imaging are currently in use. Both Pixsys, Inc. (Boulder, CO) and Northern Digital (Waterloo, Ontario, Canada) have developed digitizers based on multiple cameras fitted with linear charged-coupled devices (CCD) and cylindrical lenses that detect infrared light-emitting diodes (LEDs) or reflective devices within the surgical field (Fig. 2). As with sonic-based systems, there are line-of-sight constraints. However, systems developed by Stealth Technology (St. Louis, MO), Codman Corporation (Randolph, MA), BrainLab (Munich, Germany) and others have proven to be quick, reliable, and accurate. Multiple instruments, including the operating microscope, can be fitted with LEDs and easily tracked, as reported by Bucholz (16, 47), Zamorano (48), and Edwards (49). Theoretically, optical digitizers may be expected to be less sensitive than sonic digitizers to errors induced by the operating room environment, and this was demonstrated in one analysis (16); in practice, however, both achieve satisfactory accuracies. In another study, an optical digitizer compared favorably with a mechanical digitizer (50). It is important to note, however, that the largest contributions to overall system accuracy in the clinical setting have not been those of the particular digitizer, but those attributable to imaging resolution (i.e., slice thickness) and co-registration.

Ordinary video cameras can also be adapted for use as digitizers, as illustrated by the work of Heilbrun and colleagues (51, 52). Using two-dimensional images obtained from two different viewing angles, the three-dimensional locations of markers seen in both images can be determined. The University of Utah group has shown application accuracy comparable to that of the BRW frame (Radionics, Burlington, MA) (52).

At Dartmouth we have used a similar technique, employing high resolution (1524 by 1012 pixel CCD) Kodak DCS 200 digital cameras (Kodak, Rochester, NY) attached to the operating room ceiling on pan-tilt mounts. Interestingly, the algorithms used by such a technique are analogous to those employed by classical stereotaxy performed with intraoperative orthogonal radiographs.

Electromagnetic Field Detectors

Systems based upon a transmitter that generates an electromagnetic field, and a receiver that can be localized and oriented in three-dimensions based upon its detection of that field, offer yet another method of guidance. Since ferro-magnetic material within the operating room environment can distort the electromagnetic field, older systems — such as the Polhemus (Colchester, VT) — have generally not been well suited to surgery. A newer system based upon a pulsed DC field, and consequently less susceptible to environmental materials (Ascension Technology Corporation, Burlington, VT), is being adapted for intraoperative stereotactic purposes (Fig. 3). Manwaring (53) has described its implementation in tracking an endoscope, and we have used it for tracking an intraoperative ultrasound transducer. Kato (54) and Goerss (55) have each described adaptations such as a probe localization system, similar in function to the articulated arms in use. The method is without line-of-sight constraints and interferes minimally with the surgical field; an average error of less than 3 mm is being reported (55).

Co-registration

Independent of the type of digitizer used, all stereotactic systems require determination of the relationship between at least two different coordinate spaces. The simplest method of determining this relationship is that based upon knowing the locations in both spaces of at least three non-collinear points. This method has been used by most frameless systems and utilizes either fiducial markers placed on the patient's scalp at the time of imaging or natural landmarks, such as the nasion, lateral canthus, or tragus (3, 4, 17, 56, 57). The locations of these points on the CT or MRI scan are recorded, and at the start of the operative procedure, a digitizer is used to locate these same points in operating room space (Fig. 2B). Well-established algorithms enable one to then derive the matrix transformation or equivalent (such as direction cosines), with which one can move between the two coordinate spaces readily.

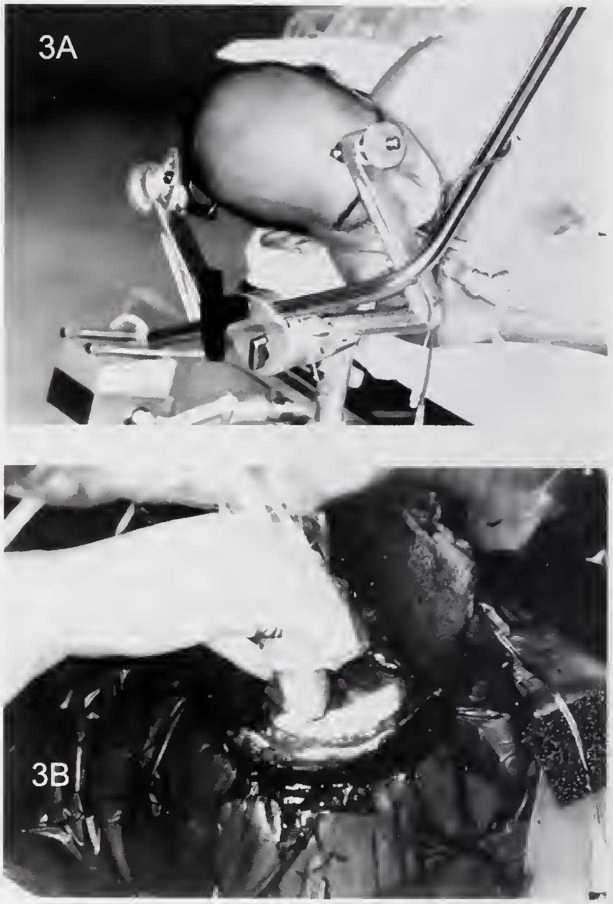

Fig. 3. **(A)** The transmitter of an electromagnetic field-sensing digitizer (The Bird, Ascension Technology Corporation, Burlington, VT) is located near the attachment of the head clamp to the table. **(B)** A small detector, here attached to an ultrasound probe, can be localized through its sensing of the electromagnetic field generated by the transmitter.

Use of natural landmarks has generally been slightly less accurate than fiducial marker techniques (which with special efforts can be made extremely accurate [58]), in large part because the former relies on usually less discretely defined points. In the recent experience reported by Golfinos (59), anatomic landmark and surface-fit algorithms achieved an accuracy approximately one-half of that accomplished using fiducial-based registration. Satisfactory degrees of accuracy can be achieved, however, and there are potential advantages to the former strategy. If the requirement for prospectively placed fiducial markers is eliminated, it becomes possible to co-register imaging studies obtained prior to the intent to operate.

Methods other than those matching sets of ordered points can also determine the relationship between one coordinate space and another. Initially for the purpose of co-registering different imaging studies with one another, Pelizzari and Chen (60) described a non-fiducial technique by which the surface contour of the head from one study could be fitted to the analogous contour from another study, much as a hat fitting a head. Others have developed similar mathematical techniques for matching surfaces, such as that used by the Analyze image processing program (The Mayo Foundation, Rochester, MN) (61). Alternatively, the curvatures inherent in the surface of a head, rather than the collection of actual points that represent the surface, may themselves be used to accomplish this matching task, as demonstrated by Friets (5). With the use of digitizing technologies such as those described earlier, surface-matching strategies can be adapted to operative planning (62) or to surgery itself. Such a registration method, of course, can be used in combination with a fiducial-based algorithm to optimize the step even further, as is possible with the ISG Viewing Wand (ISG Technologies, Mississauga, Ontario, Canada) (63). This ability to match surfaces or contours can be used with any number of digitizing modalities, including articulated arms, sonic digitizers, optical systems, and electromagnetic sensors. All that is required is digitization of a sufficient portion of the surface to enable reliable matching with the surface derived from preoperative imaging data.

From an efficiency perspective, the strategy of employing non-contact digitizers, which can collect necessary data in a more automated fashion, has great appeal. Video camera and electronic camera systems, such as those developed by Heilbrun et al. (52), at Dartmouth, and by Gleason et al. (64), have demonstrated the ability to capture sufficient contour and surface feature data to permit co-registration with MRI or CT studies. Laser range finders may be used similarly for this purpose. The sophistication of co-registration strategies and algorithms is evolving rapidly (65), and the accuracy, time efficiency and degree of automation are constantly improving.

Stereotactic Display and Effectors

Having accomplished co-registration of image and surgical coordinate spaces, stereotactic systems must then make the derived information available to the surgeon in a useful manner. Our operating microscope accomplishes this with a small monitor attached to the microscope through a beam-splitting assembly (3, 5); Kelly has developed a similar interface (66). The resultant heads-up display enables the surgeon to see both the conventional surgical field and the superimposed, computer-generated graphics. The default option in our system displays the intersection of the focal plane of the microscope and any object of interest, such as a tumor, so that the segmented structure is depicted in the correct location, orientation and scale. Alternatively, any other parallel plane may be superimposed, an often-used option in getting to a lesion. Should the targeted object be out of the field of view, the system can display a graduated line connecting the focal point (in the center of view) and the projection of the center of gravity of a deeper object into the focal plane. Wall monitors display appropriate CT or MRI images in which the microscope's focal point is represented by a cursor.

Those frameless stereotactic systems that track hand-held pointers or instruments provide feedback to the surgeon with similar external monitor graphics. Multiplanar displays showing annotated axial, coronal, sagittal and reformatted "down the trajectory" planes as well as three-dimensional renderings, with and without cutaway views, all provide easily used assistance (Fig. 4). Displays of planes perpendicular to the optical axis of the operating microscope or the long axis of an instrument, and accompanying views parallel to that axis in several planes, can be useful in understanding what lies along a specific trajectory. Comprehension of such data, however, is sometimes difficult and non-intuitive in unorthodox, oblique planes. The ability of a display to provide the surgeon a choice among options based upon both the patient's and the tool's coordinate systems is highly desirable.

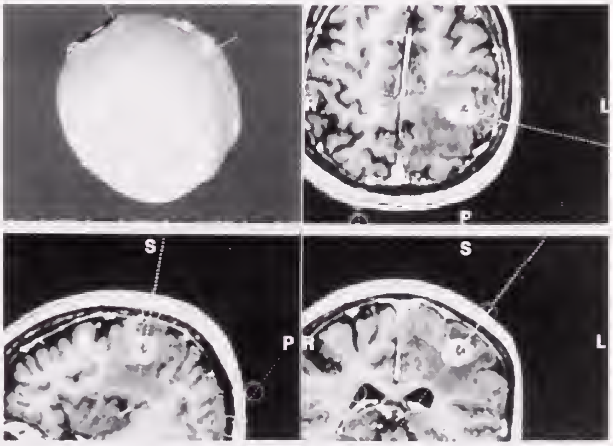

Fig. 4. (Top left) Reconstructed skull for planning burr holes. (Top right) Axial view of left (L) parietal (P) tumor. (Lower left) Suggested route (S) in sagittal view of parietal (P) lesion. (Lower right) Suggested route (S) in coronal view of enhancing left (L) tumor.

Clinical Applications

While feasibility and accuracy assessment have been appropriate goals of early work, clinical experience with frameless stereotactic systems has been growing. Practical intraoperative utility has been favorable in early reports, and useful applications across a wide spectrum of procedures are being described (10, 12, 59, 67). Access to the structural lesion, defining the extent of the resection and thereby assuring completeness of intended surgery, and protecting non-pathologic critical structures are all useful and accepted principles in any surgery. These principles are of central importance to those oriented toward minimally invasive surgery, and each is more attainable through the techniques of surgical navigation. Below is an examination of the techniques described above, in their application to a variety of clinical settings.

Intracranial Neoplasms

Surgery for the resection of subcortical and deep tumors has perhaps been the most common application of frameless navigation (10, 12, 14, 35, 40, 56, 66, 68, 69). This application extends common stereotactic localizing capabilities to open craniotomy, and a variety of benefits are derived. Preoperatively, precise determination of the location of the tumor and planning of a trajectory to approach the lesion are carried out on a graphics workstation. Once co-registration has been performed in the operating room, stereotactic guidance can direct the location and extent of craniotomy. The location, shape, and size of the skin incision and bone flap can be tailored to minimize the overall exposure.

Surface features of the cortex can be predicted, allowing vascular structures to be avoided and even excluded from the opening. Once exposure of the cortical surface is complete, navigational systems can direct the surgeon to the optimal cortical incision along the predetermined trajectory, by means of the graphics display or, in some systems, following lasers illuminating the trajectory to the focal point. Progress toward the lesion can be monitored dynamically on the computerized imaging studies.

Upon arrival at the lesion, the resection can be guided by these same techniques. A navigation system can track the location of a surgical instrument and map the instrument's location to the imaging studies, or alternatively, the position of the microscope itself can be tracked, allowing for localization of the focal point. Using this technique, the visual field is directly mapped to the imaging study. With either method, progress through the resection can be monitored and non-pathologic structures avoided. For both assessment of complete resection and avoidance of normal tissue, the surgeon's accuracy and efficiency are enhanced.

Vascular Malformations

Vascular applications with reasonably well understood anatomic relationships, such as aneurysm clipping, might be expected to gain less from stereotactic guidance. Derived benefits may be less apparent for surgery in the extra-axial spaces where normal landmarks may be available to assist orientation. Nevertheless, these interventions may benefit from recent advances in computer visualization of the pathology (70).

Vascular malformations, on the other hand, represent less-stereotypical pathology. Arteriovenous malformations (AVMs), with their individualized feeding and draining vessels, are associated with a sustained risk of hemorrhage. Cavernous malformations, though their natural history is less well understood, can also present a challenge when symptomatic, because of their location. Vascular malformations may lie in close proximity to eloquent areas of cortex or deeply, where access to the lesion may necessitate traversing functional neurologic tissue. Surgery in either of these locations carries risk of neurologic deficit, but is often the management of choice. Surgical navigation can play a role in decreasing this surgical morbidity. Several reports have demonstrated the efficacy of these techniques on such lesions (14, 70–75).

In the case of the surface AVM near eloquent regions such as speech or motor centers, the incorporation of functional imaging data can enhance the ability of the surgeon to avoid these critical regions. Functional imaging such as positron-emission tomography (PET) scanning or functional MRI can be co-registered with other imaging data, as well as the patient. Another technique integrates image guidance with intraoperative functional mapping. The bipolar stimulator used to determine motor, sensory, and language areas during mapping can be localized on the imaging studies, and an integrated database developed. Preoperative planning may also help with the identification of vascular structures on the cortical surface, and recognition of these landmarks intraoperatively can give the surgeon additional confidence. With deep-seated AVMs, target trajectory techniques, as described for subcortical tumors, are useful in guiding the surgeon to the lesion with minimal disruption to surrounding normal brain. With an accurate trajectory, the opening as well as the surgical corridor can be kept to minimal size.

Epilepsy

Open functional surgery in general, and surgery for epilepsy specifically, are particularly well suited to computer-assisted, stereotactic techniques. The identification of a seizure focus and its excision with preservation of normal function often requires the surgeon to remove tissue that is visually indistinguishable from normal brain. This may at times be the surgical equivalent of "flying blind." Therefore, the integration of multiple imaging modalities and electrophysiologic data into a navigational system can be more helpful than in any other surgical procedure.

Surgical navigation techniques can be used in both the evaluation and the treatment of patients with medically intractable epilepsy (67, 76–79). For patients whose seizure focus is difficult to localize, the co-registration of preoperative imaging such as high-resolution MRI and physiologic studies such as PET, ictal single photon emission computed tomography (SPECT), and functional MRI can help with the planning and accurate placement of invasive recording electrodes.

In those patients in whom the seizure focus has been accurately mapped to the cerebral cortex by invasive monitoring, additional steps can be taken to assure the accuracy of resection. A postoperative CT scan with the electrodes in place, routinely obtained and co-registered with the previous database for that patient, enables the navigation system to identify the contacts that overlie the seizure focus intraoperatively. All of this can be tailored to the individual patient, a feature critically important in neocortical epilepsy.

In cases where epilepsy is thought to be secondary to a lesion, the trajectory planning features of the surgical navigation system direct the surgeon to that lesion with equal accuracy, as described above for subcortical tumors or deep-seated vascular malformations. Selective amygdalohippocampectomy is similarly benefited. This procedure can be accomplished through an enlarged burr hole and can replace a temporal lobectomy in selected cases.

The Spine

The greatest challenge for frameless applications in the spine has been in co-registration. The inability to fix external fiducials and the non-rigid relationship between multiple spinal segments reliably or easily has precluded methodologies used for cranial procedures (7). Co-registration for the spine is most easily done through exposed bony structures during surgery, with registration of each segment performed independently. These landmarks can be seen clearly on preoperative imaging studies and, once exposed, work well for co-registration purposes.

The goal of surgical navigation in the spine, as in intracranial work, is the localization and orientation of structures not visible in the surgical field. Although localization of tumors and fracture fragments in the spine can be done, the predominant application in spinal surgery has been in assisting placement of pedicle screws. This procedure has traditionally been done with the guidance of intraoperative radiographs or fluoroscopy, but these additional studies can be time consuming and inadequate for accurate placement. Surgical navigation takes advantage of the preoperative imaging and offers the additional benefit of three-dimensional visualization. After bony exposure and registration, a tracked probe or drill guide is adjusted until aligned with an optimal trajectory. Coupled with depth estimates, the final location of the screw can thus be predicted (80–82).

Endoscopy

Rigid endoscopy lends itself well to frameless stereotaxy, since orientation of the often restricted visual image can be facilitated by integration with standard radiologic studies (53, 83). Flexible endoscopes are obviously more problematic. However, this type of guidance can be helpful in terms of performing tumor biopsies or third ventriculostomies. The information available through the navigation system adds an additional degree of confidence concerning actual location. Another example that has been described is that of fenestration of loculated hydrocephalus. This is a challenging disorder for endoscopic treatment because, though the endoscope is less invasive, the potential for disorientation is high. If the navigation system can help in the preoperative planning of a single trajectory that will encounter all of the cysts and enable them to be fenestrated sequentially, the concerns for disorientation and incomplete treatment can be greatly reduced. Interestingly, the intraoperative utility of the navigation system is reduced in this situation because of the significant amount of movement of intracranial tissue during this procedure, with resultant loss of initial co-registration. Nevertheless, the preoperative planning may have already improved the potential outcome.

Future Directions

Current advances in frameless stereotaxy include improvement in the efficiency and accuracy of registration (84), strategies to cope with intraoperative brain displacement and deformation ("shift") (85), and refinement of information display systems (86, 87). Those settings in which structures within the surgical field may have deformed or shifted in relation to the original registration features are not accounted for by the above co-registration methodologies. The error arising from such movement may be accounted for through re-imaging, re-registration, or both. Digitization of the same or different registration points (either by the same digitizing technology or through the use of different intraoperative imaging devices, including cameras, ultrasound, or even CT and MRI scanning) is being investigated. Through interpolation or predictive modeling techniques, less resolved (and consequently less expensive or constraining) imaging modalities may be satisfactory for this purpose.

A variety of workstation applications, as well as viewers, goggles and helmets developed for virtual reality or augmented reality (in which real perception is also preserved, as in a microscope's heads-up display) applications, are also becoming available. Sophisticated graphics, with three-dimensional renderings, appropriate segmentation, variable transparencies, fused imaging modalities, and manipulable scale and perspective can assist structural understanding and surgical planning considerably. Simulation of the surgeon's intraoperative perspective during actual surgery, as implemented by the Brigham group (63), functions as a navigational guide in itself.

Conclusion

The power of frameless stereotaxy has already evolved to a point where its use enables the surgeon to be minimally invasive. Improved planning leads to smaller incisions. Improved navigation helps prevent injury to local structures. Improved target localization ensures confidence in the completeness of a surgical resection. All of these can improve the quality of care, decrease operative time, and lower expenses.

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Continuing Experience with Chemonucleolysis

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Abstract

Chemonucleolysis using chymopapain is the least invasive technique used to treat a herniated lumbar pulposus. After 37 years of clinical experience, multiple clinical trials, a national multicenter, double-blind study mandated by the Food and Drug Administration, and heated controversy in the scientific community, the injection of chymopapain to treat herniated discs has (in appropriately selected patients) proven as successful as laminectomy, with fewer complications and the advantage of considerable cost savings. **Key Words:** Herniated lumbar disc, chemonucleolysis, chymopapain.

IN 1963, LYMAN SMITH (1) was the first to inject chymopapain for the treatment of unremitting sciatica due to a herniated lumbar nucleus pulposus; he coined the term "chemonucleolysis" (CNL) for the procedure. Even after 37 years of clinical experience with CNL, the administration of chymopapain still provokes controversy, especially among those with very strong opinions who have never used the enzyme. Nevertheless, this minimally invasive technique has been the most studied, the most evaluated, the most regulated, and the most closely followed therapy for unremitting sciatica ever utilized by the medical profession.

Pharmacology

Chymopapain is a proteolytic enzyme derived from papaya latex. It acts as a catalyst which promotes rapid hydrolysis of the chondromucoprotein portion of the nucleus pulposus (2). Although the specific substrate(s) remain obscure, it is known that the enzyme inhibits the ability of proteoglycan to adsorb water which then leads to a breakdown of cartilage. Similarly, since proteoglycans are crucial in maintaining the integrity of vascular endothelial lining, chymopapain may cause bleeding from the microcirculation if it comes in direct contact with the capillaries. Large vessels are not affected. Recent studies also indicate that chymopapain modulates the activity of phospholipase A and thus exhibits anti-inflammatory qualities (3).

Indications

Proper patient selection is paramount for the success of chemonucleolysis. Only 10% of patients with unremitting sciatica and neurologic changes due to a herniated nucleus pulposus should be considered for discectomy or chemonucleolysis if they do not respond to conservative treatment (4). Not all laminectomy candidates are suitable for chemonucleolysis. Classic indications are symptomatic lumbar disc displacement as indicated by MRI, CT, and/or myelography, and lack of other major cause of symptoms. Conservative treatment should be attempted for a minimum of 6 weeks.

A recent study indicates that the size of the herniated disc is not a factor for a satisfactory outcome, nor is the shape of the spinal canal (5). The disc does not have to be contained; however, a sequestrated fragment in certain cases may be a contraindication. Age can be a factor, because patients over 60 years of age may lack sufficient

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mucoprotein for the herniated disc to be hydrolyzed. Among patients younger than 20 years, an 80–90% success rate has been reported (6). A good candidate is one with single level involvement, leg pain exceeding back pain, and good correlation of the findings on physical and imaging examinations.

Contraindications

Known contraindications include: (a) allergy to papaya or papain, (b) pregnancy, (c) severe or progressive neurologic deficit, (d) cauda equina syndrome, (e) arachnoiditis, (f) diabetic polyneuritis, (g) spinal tumors, (h) central or lateral recess spine stenosis, (i) migrated disc, (j) severe spondylolisthesis, and (k) history of discitis. Chemonucleolysis is also contraindicated for patients with recurrent disc herniation after surgery at the same level. Repeat chemonucleolysis is not approved by the FDA.

Clinical Studies

In 1975, when FDA approval of chymopapain was sought, 17,000 patients had already been injected. Nonetheless, some surgeons insisted that a double-blinded study must also be done, to eliminate the possibility of the placebo effect. Others thought this to be contrary to the Helsinki Accord, in which the use of a placebo was strongly criticized in any research study where specific treatment was known to be effective. A multicenter, double-blind study was done in 1981, and the results were reported in *JAMA* in 1983 (7), with a 75% favorable response to the enzyme versus 45% to placebo. To our knowledge, this was the first double-blind study of treatment for a musculoskeletal disorder. Subsequently, a double-blind study in Australia was reported by Gogan et al. (8). In 1988, Dabezies et al. (9) reported a study done in the United States. Both showed positive results for CNL. Ramirez and Javid reported good or excellent results for laminectomy in 77% of their cases (10).

Our prospective one-year study with follow-up of 100 consecutive patients (including 22 workers' compensation cases) who underwent CNL, and 100 consecutive patients (including 24 workers' compensation cases) who underwent laminectomy yielded the following results (11):

At 6 weeks (Figure), the success rate for CNL was 80% (excellent 33%, good 47%). For laminectomy, it was 85% of patients (excellent 52%, good 33%). Although statistically these results seem to favor laminectomy, p = 0.013, improvement in sciatica was similar in both groups. Slight improvement occurred in 7% of CNL patients and 6% of laminectomy patients; 10% of CNL patients and 3% of laminectomy patients remained unimproved.

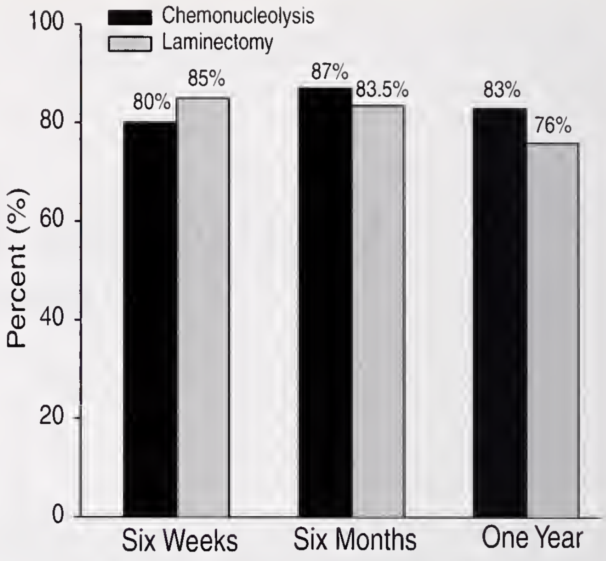

Figure. Comparison of overall successful results of chemonucleolysis versus laminectomy.

At 6 months (Figure), results were good-to-excellent for 87% of 100 CNL patients, and for 83.5% of 97 laminectomy patients; 4% of CNL patients and 6.1 % of laminectomy patients showed slight improvement; 9% of CNL patients and 5.1% of laminectomy patients showed no improvement; and 4.3% of laminectomy patients had deteriorated to preoperative pain levels.

At one year (Figure), results were good-to-excellent for 83% of 100 CNL patients and for 76% of 97 laminectomy patients who were available at one year; 7% of CNL patients and 14.5% of laminectomy patients showed slight improvement; 10% of CNL patients and 9.5% of laminectomy patients showed no improvement.

There are no statistically significant differences between the two groups. In addition, long-term experience with CNL has repeatedly shown lack of postoperative fibrosis and maintenance of successful results over many years.

Complications

Earlier, anaphylaxis had been a concern, following its occurrence in 0.5% of cases, mostly in the southern states. But, with IgE, chymopapain sensitivity testing and administration of antihistamine agents prior to use, anaphylaxis has been reduced to 0.25% of total allergic reactions in the United States; it is even lower in Europe. There have been no major anaphylactic complications since April 1987, although seven deaths from anaphylaxis occurred prior to that time.

Since the enzyme is under the jurisdiction of the FDA, all reactions following CNL administration must be reported within 15 days. (This is not true of laminectomy.) The total thus far includes 121 adverse reactions in about 135,000 patients. We often read that chymopapain results in more complications than does laminectomy/discectomy. Actual comparison of usual complications, however, reveals 17 times more infections, 6 times more neurological and vascular problems, and an overall mortality 3 times greater in laminectomy than in CNL (12). In a European study (13) of 43,662 chymopapain-injected patients and 2,051 discectomy patients, ten times as many complications occurred in the open surgery as in the CNL cases.

Reinjection of chymopapain has always been prohibited in the United States, because of fears of sensitizing the individual and thereby creating a greater probability of anaphylactic reactions. The International Intradiscal Therapy Society sponsored a study of 420 reinjected patients in 1997. Five cases had minor reactions that needed no definitive treatment, three had some decrease in blood pressure and transient distress, and one had a full-blown anaphylactic shock that responded to treatment. Two smaller studies came to conflicting conclusions (14, 15). With the availability of IgE chymopapain testing, there is no reason to withhold CNL from these patients. Our own experience with repeat injection in four patients with recurrent disc herniation at the same level and in two patients with the problem at another level revealed no allergic reactions.

Efficacy and Future

The continued practice of chemonucleolysis is dependent upon surgeons who have seen the results personally and are well versed in the body of medical literature supporting the procedure. The responsible use of chemonucleolysis and chymopapain is paramount. From the double-blind (7) and longitudinal (16) studies and the recent article by Postacchini (17), it is clear that chemonucleolysis and chymopapain are safe and effective in the treatment of lumbar disc herniations for patients who are carefully selected and screened.

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Anterior Cervical Discectomy without Fusion or Instrumentation:

25 Years' Experience

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Abstract

Objective: To assess a minimalist approach to anterior cervical discectomy without instrumentation or bone grafting.
Method: A total of 530 operations performed during a 25-year period were evaluated in terms of technique and patient outcome.
Results: Advantages included minimal blood loss, little tissue swelling, less narcotic requirement, fewer days in the hospital, and earlier return to customary activity. During the 2-year follow-up period, a repeat surgical procedure was required in only 2% of the group.
Conclusions: Eliminating spinal fusion from anterior cervical discectomy shortened the operation, reduced the number of surgical instruments needed, and eliminated complications associated with obtaining a graft from the iliac crest or maintaining the bone *in situ*. **Key Words:** Intervertebral disc, cervical vertebra, microsurgical technique.

CLOWARD (1) AND SMITH AND ROBINSON (2) performed anterior discectomy, employing grafts from the ilium, without microsurgical technique for magnification and illumination of the structures of the intervertebral disk space. Fusion was counted upon both to encourage absorption of existing osteophytes and to discourage future osteophyte formation in the foraminal areas. In 1975, Hankinson and Wilson (3) removed herniated cervical discs with the operating microscope but without fusion; the results without a bone graft were entirely comparable. More recently, instrumentation with plates and screws has been used in addition to bone grafts for early stabilization (4). The purpose of this paper is to report a series of 530 anterior cervical discectomies performed over a 25-year period without fusion or instrumentation.

Materials and Methods

The ages of the patients ranged from 19 to 82. A total of 302 men and 228 women came to surgery (Table); 30% were compensation cases. The cases with 4 separate herniated discs underwent separate operations for the 2 superior and 2 inferior levels.

The surgical technique (Figs. 1A and 1B) has previously been published (5). All the patients referred for surgery had radicular pain unrelieved by conservative treatment including traction for at least 6 months, and/or objective findings on neurological examination, such as motor or reflex deficits. MRI (Fig. 2) was performed in every case; over the 25 years, fewer and fewer patients underwent preoperative study by CT as well. Review of the neuroradiologic studies accurately predicted the operative findings.

With the advent of managed care, discharge following surgery has occurred most often on the day following surgery, as long as the dysphagia was minimal and oral intake was adequate. With continuous wearing of a soft collar, the patient

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TABLE

530 Patients with Herniated Cervical Discs

One Level	n	Two Levels	n	Three Levels	n	Four Levels	n
C3-4	11	C4-5+C5-6	70	C4-5,C5-6,C6-7	10	C3-4,C4-5,C5-6, C6-7	2
C4-5	110	C5-6+C6-7	82				
C5-6	153						
C6-7	92						

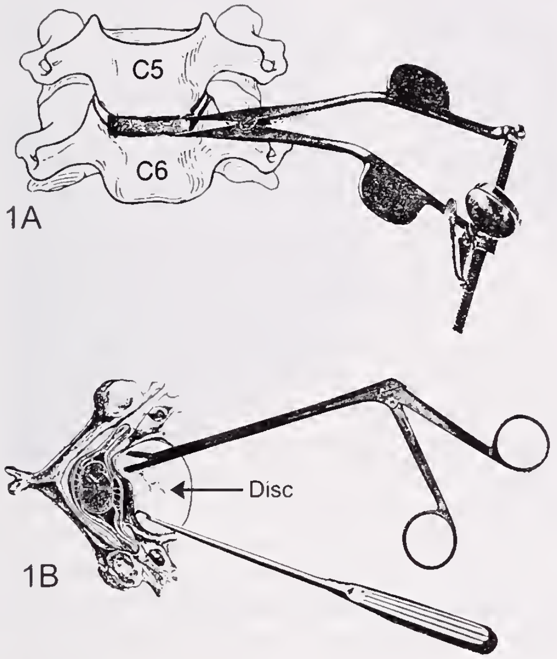

Fig. 1. **(A)** Artist's drawing of Cloward vertebra spreader in place. **(B)** Axial view of Cloward forceps and microcurette within a disk space containing a herniated nucleus pulposus.

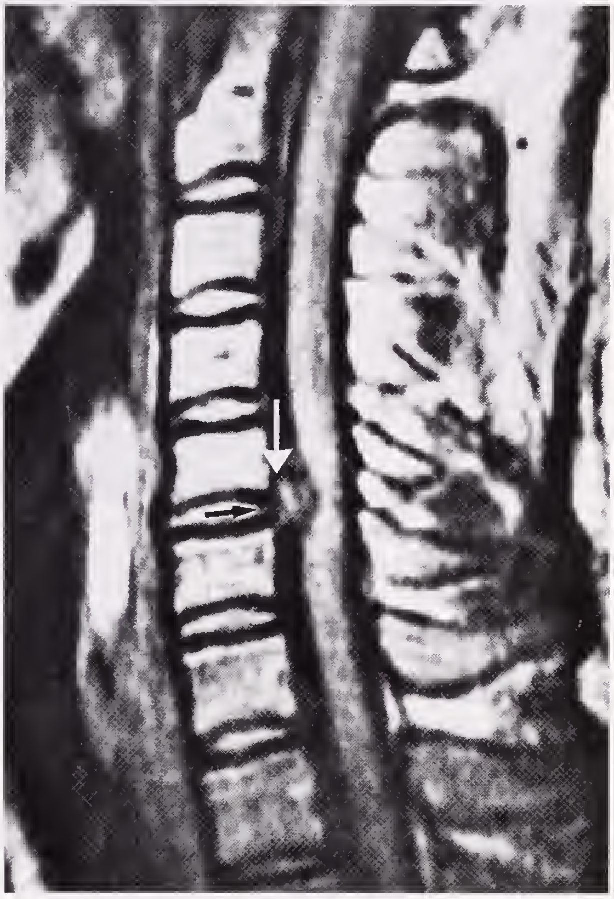

Fig. 2. Preoperative MRI shows disc herniation (arrow) at the C5-6 level.

was not confined to bed rest. Advice was given about performing normal activity, showering, and avoiding driving. A follow-up visit was scheduled after 3 weeks of convalescence at home. Wearing of a collar was tapered over another month. Instruction in corrective exercises was offered, and regular evaluation was done at 2-month intervals for at least one year.

Results

No complication of increased neurological deficit, wound infection, cerebrospinal fluid fistula, direct damage to the esophagus or trachea, or hemorrhage requiring transfusion occurred in my series of 530 anterior cervical discectomies. Three cases of Horner's syndrome were observed, but all resolved within 3 months. Two cases of thrombophlebitis were diagnosed; readmission and prolonged hospitalization with anticoagulation therapy were prescribed without further complications. One 68-year-old woman who underwent surgery at the C5-6 level developed discitis; with prolonged immobilization in a plastic, molded, posted collar, her pain resolved after fusion took place.

One 48-year-old man who was discharged within 24 hours developed shortness of breath after an episode of prolonged coughing at home; CT (Fig. 3) on readmission documented a prevertebral hematoma causing tracheal and carinal compression. Even though his oxygen saturation never dropped below 98%, tracheostomy and reexploration for evacuation of the 50 cc hematoma were necessary because of stridor and

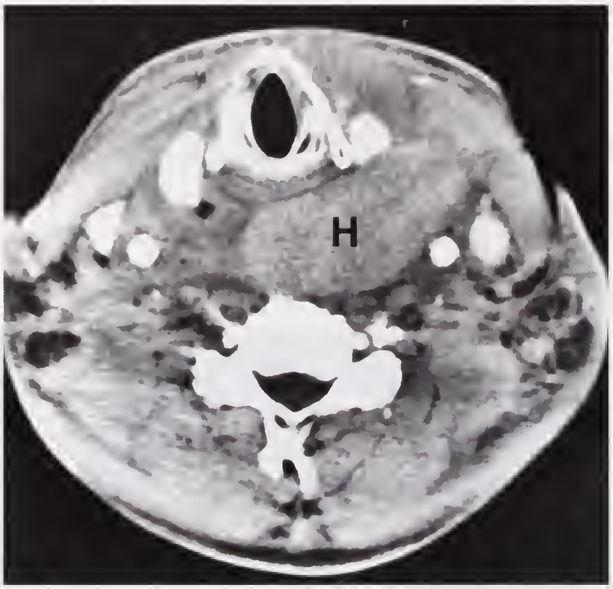

Fig. 3. Postoperative CT of the cervical spine shows the prevertebral hematoma (H) compressing the trachea.

anxiety. The patient was extubated and able to return home in less than 7 days after his original surgery.

Preoperatively, almost all of the patients were debilitated by muscle spasm in their neck and shoulder girdle. Postoperatively, every patient was ambulatory and able to be evaluated at an office visit. In each case, the question was asked, "Are you better?"; 490 replied affirmatively, and 40 said, "No."

The patients who were not improved were reevaluated by MRI; the neuroradiologic imaging revealed postoperative changes at the appropriate level. Twelve patients were reexplored. The fusion and scar made dissection technically difficult. The incision was made to the right of the midline, and disarthrodesis was accomplished with a small power drill. Re-formed osteophytes were found to compromise the foramina. Eight of the 12 patients who underwent second surgery improved symptomatically after reexploration.

Discussion

Eliminating spinal fusion from anterior cervical discectomy has shortened the time required for surgery, reduced the number of surgical instruments needed, and eliminated complications associated with obtaining a graft from the iliac crest or maintaining the bone *in situ*. Microscopic technique involves careful study of the preoperative neuroradiologic studies, planning small incisions and precise anatomical approaches, and optimal use of magnification and illumination. Operations requiring 60 minutes or less are associated with very low rates of postoperative complications.

The incidence of discitis in the cervical spine (Fig. 4) is far less than in the lumbosacral area, even though the cartilaginous plates of the disk space are regularly scraped with curettes. Horner's syndrome results from manipulation and traction on the cervical sympathetic chain. Some settling of the vertebral bodies, anterior rather than posterior, occurs after discectomy without fusion. The neural foramina may become narrower unless adequate foraminotomy has been performed bilaterally. Spontaneous arthrodesis of the adjacent vertebrae can be verified by flexion and extension x-rays 8 – 12 weeks postoperatively (Fig. 5A and 5B).

In 1995, Gaetani et al. (6) retrospectively analyzed the clinical long-term results in 153 patients who underwent discectomy without fusion. Excellent or good results were recorded in 91% of the 108 cases with radiculopathy and 58% of the cases with myelopathy. The authors concluded that presentation with pure radicular signs was the most important factor in predicting the surgical result.

In 1998, Savolainen et al. (7) reported a prospective randomized study on the surgical results of 91 patients with single-level cervical root compression. The clinical outcomes were

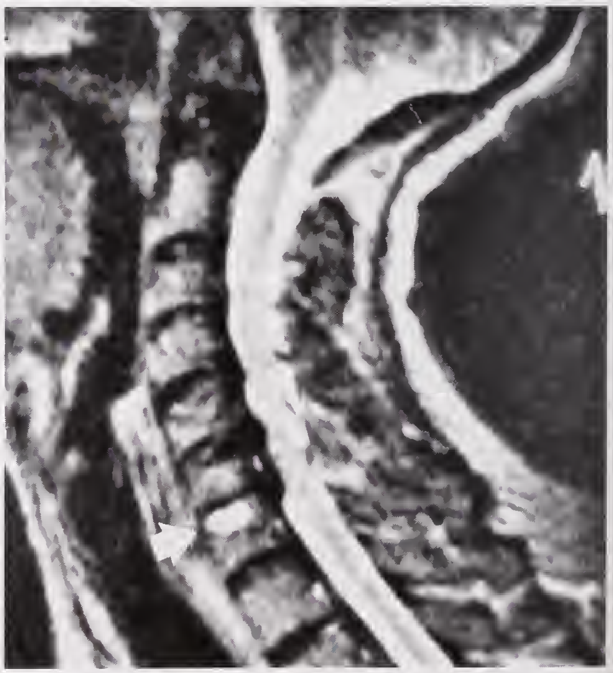

Fig. 4. Postoperative MRI. Note area of increased signal density (arrow) representing inflammatory process of disc space.

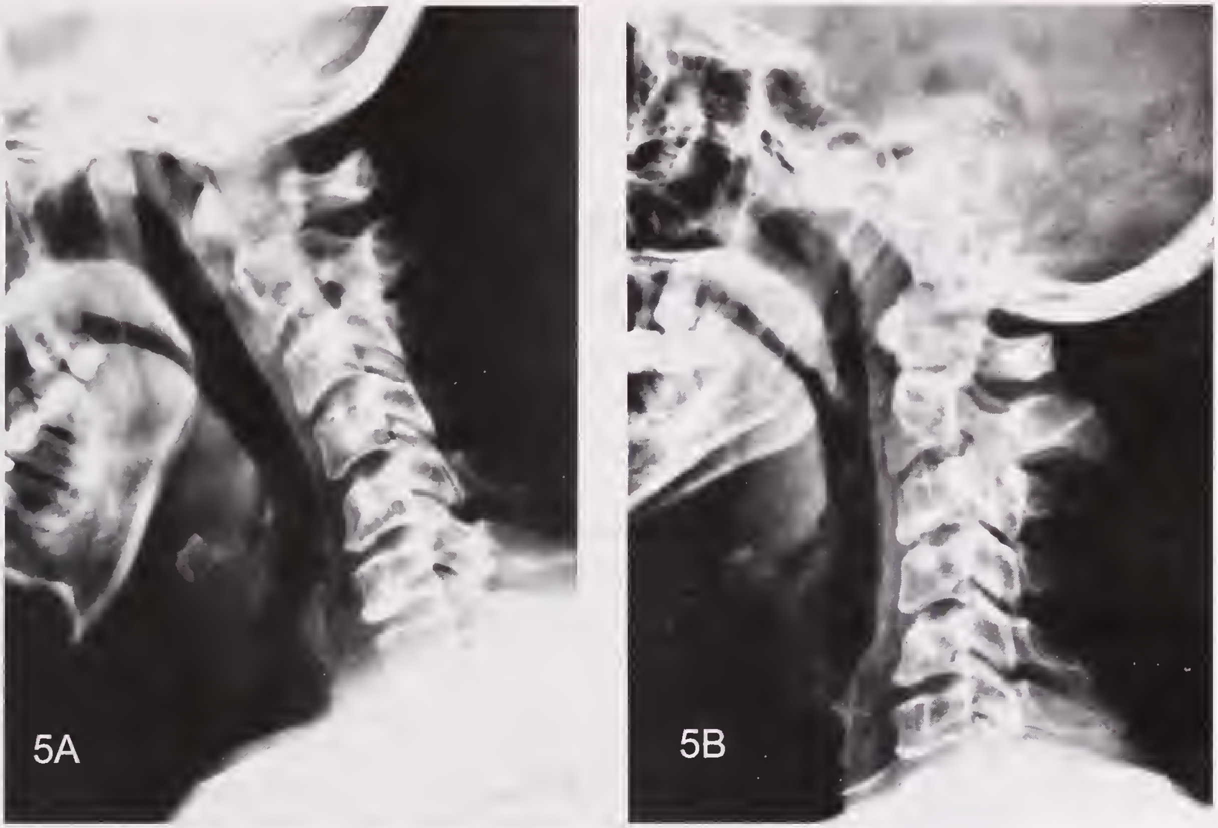

Fig. 5. (**A**) Lateral flexion and (**B**) extension x-rays demonstrating postoperative changes and lack of motion at the C5-6 level.

good in 76% of patients treated by simple discectomy, 82% of patients who received bone grafts, and 73% of those who underwent fusion plus plating. Poor results were observed in 0%, 4%, and 4% respectively. They concluded that satisfactory outcomes could be achieved by simple anterior discectomy without fusion or instrumentation.

The most recent retrospective research into the long-term benefit following cervical disc surgery with and without bone graft placement was conducted by questionnaires. In 1998, Thorell et al. (8) reported evidence that patients who underwent fusion did better in terms of pain and normal function. Nevertheless, the published reviews at the end of the article did not agree with these authors' conclusions.

Summary

The minimalist approach to cervical discectomy requires a small number of Cloward instruments, a power drill, fiberoptic headlight, and binocular loupes. The issue of the role in outcome of the use of a bony intervertebral spacer continues to be investigated. Good results (92%) and low rate of second surgery (2%) were recorded in a series of 530 patients who underwent neurosurgical intervention without fusion over a 25-year period.

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CT-Guided Needle Procedures for Brain Lesions:

20 Years' Experience

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Abstract

Objective: To assess free-hand needle procedures with CT guidance for biopsy and drainage of brain lesions.

Method: A series of 184 operations was carried out on 120 patients over a 20-year period. Sixty (60) cases of suspected neoplasm were biopsied; 40 cases of intracerebral hemorrhage and 20 cases of intracranial suppuration underwent drainage.

Results: The morbidity and mortality of the methods described were quite low due to steroid therapy, prophylactic antibiotics, and careful preparation of the access site. There was one complication of postoperative hemorrhage in a patient with metastatic melanoma.

Conclusions: The simple and accurate techniques presented continue to have widespread application in the practice of neurosurgery and compare quite favorably with techniques using more elaborate equipment, stereotactic frames, and intraoperative monitoring. **Key Words:** Computerized tomography, brain neoplasm, cerebral hemorrhage, brain abscess, brain biopsy.

SHORTLY AFTER THE ADVENT OF computerized tomography (CT), Maroon (1) performed needle biopsy on brain tumors and monitored the technique by intraoperative imaging. Drainage of intracerebral abscesses (2, 3) and hematomas (4) was subsequently reported at other major medical centers. Additional small series appeared in the medical literature (5 – 10) until 1992, when three neurosurgeons in suburban practice published articles on a series of 147 patients (11, 12). The author has personally performed 184 free-hand procedures with CT guidance over a 20-year period. The purpose of the study described here was to assess this procedure, based on the author's experience.

Materials and Methods

The patients were divided into three groups: 60 cases of suspected neoplasm, 40 cases of intracerebral hemorrhage, and 20 cases of intracranial suppuration. Most of the hematomas and abscesses required more than one tap, but only 5 tumors required a second biopsy.

After review of the initial diagnostic CT, a limited study was repeated for the purpose of marking the scalp over the intracranial mass. Indelible ink recorded the laser beam in plane with the scan that visualized the largest diameter of the mass. The trephine site was placed as close to the lesion as possible, but within the hairline and away from sensitive areas of the cortex.

In the operating room, a burr hole was made under local anesthesia, in most cases; general anesthesia was employed when the patient could not cooperate. The dura was incised in a cruciate fashion, and the pia-arachnoid was coagulated with a bipolar forceps before being opened with a small scalpel. Biopsy or drainage of a mass close to the surface was attempted immediately in 79 cases. After closure of the skin, 41 patients with deep-seated lesions were taken back to the CT scanner and underwent a third imaging procedure to visualize the relation of the burr hole to the

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mass and to monitor insertion and placement of the needle. Correct positioning of the needle was accomplished on the first try about 80% of the time; a second pass was successful in the remaining cases. The closed skin of the incision held the needle steady during the procedure. Serial scans evaluated any intraoperative bleeding.

For biopsy of a suspected neoplasm, the software component of the CT scanner measured the depth and angle of the mass lesion from the surface of the scalp over the burr hole (Fig. 1A). A 13-gauge Field-Lee needle, consisting of four coaxial components, provided a guillotine-like effect when the inner hollow cannula with a window was withdrawn in conjunction with suction provided by a glass syringe. Taking out the metallic components during the procedure allowed the plastic radiopaque sleeve to be viewed with little artifact (Fig. 1B). The small amount of air which entered the needle provided accurate localization of the exact biopsy site. A frozen section confirmed the histologic diagnosis of brain tumor.

Evacuation of an intracerebral hematoma (Fig. 2A) was accomplished by a 13-gauge, two-hole Cone ventricular needle in conjunction with a glass syringe for suction. Drawing from opposite sides of the blunt needle and at two separate depths minimized the need for repositioning to empty the collection of blood. The artifacts created by the stainless steel needle did not interfere with monitoring of the drainage (Fig. 2B). Removal of 30–50 cc of semisolid clot was readily accomplished.

The capsule and cerebritis surrounding a brain abscess were best demonstrated by intravenous injection for CT imaging (Fig. 3A). The same two-hole Cone needle was used to draw off purulent material (Fig. 3B). Gram stain was performed immediately, and aerobic as well as anaerobic cultures were begun. The amount of residual air or air-fluid level documented emptying and shrinkage of the abscess cavity.

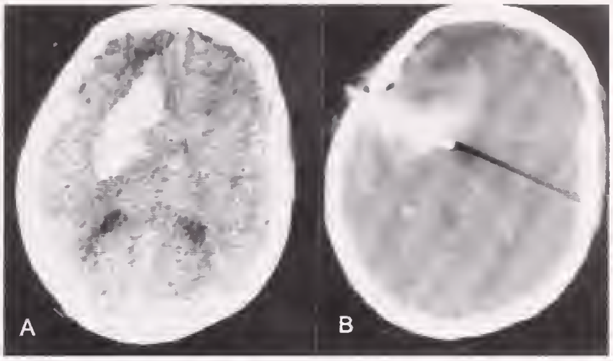

Fig. 2. **(A)** Large, irregular, high-density area of hemorrhage (white irregular mass) in hypertensive patient; no contrast media was necessary. **(B)** Metallic artifact has been reduced by manipulating the window of the scanner (out of focus).

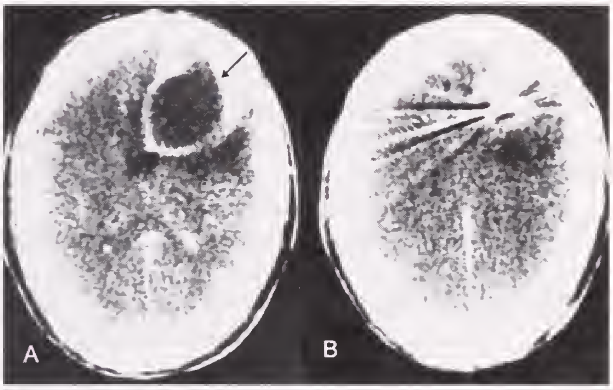

Fig. 3. **(A)** Right frontal abscess 50 cc in volume (black circular area — arrow), outlined by enhancing white rim. **(B)** Needle artifact does not interfere with location of tip (out of focus).

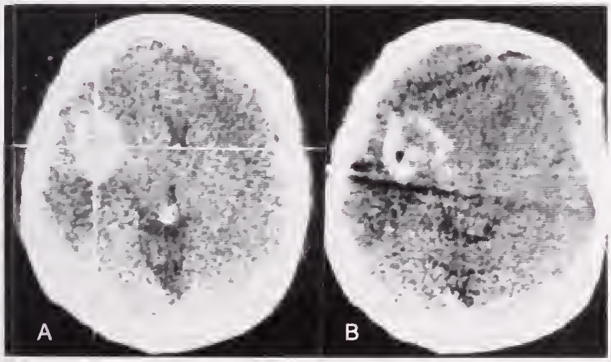

Fig. 1. **(A)** Highly dense circumscribed lesion after intravenous injection of contrast media. Only the transverse measurement was available (note lines), but any angulation could be easily calculated. **(B)** Low density of air shadow within tumor (small black area) identifies site of biopsy.

All of the patients received high-dose steroid therapy. Intraoperative prophylactic antibiotics were employed in the clean cases. Therapeutic doses of broad-spectrum antibiotics were begun as soon as the diagnosis of brain abscess was suggested on initial CT scans.

Results

Of the 62 suspected tumors in 60 patients, 57 were diagnosed by needle biopsy (Table 1). Early treatment with radiation and chemotherapy was instituted in 55 cases of confirmed tumor. In five cases, the specimens were suggestive of a primary neoplasm after two separate biopsies per case, but gliosis could not be ruled out; the patients underwent subsequent craniotomy and excision of low-grade astrocytomas.

TABLE 1
Sixty-two Mass Lesions in 60 Patients (67 Procedures)

33 gliomas
16 metastases
6 cerebral infarcts
1 meningioma
1 cysticercus cyst
5 gliosis (biopsied twice)

Forty cases of intracerebral hematoma required 75 drainage procedures (Table 2). The second needle procedure was scheduled 24 hours after the first drainage in 35 cases. Twenty patients improved after evacuation and 20 were unchanged.

All of the brain abscesses (Table 3) resolved after drainage and 8 weeks of appropriate antibiotic therapy dictated by serial culture and sensitivity testing. Seventeen large lesions were drained twice, and one solitary lesion required only one procedure. Two patients developed multiple small areas of intracerebral purulence after undergoing extensive craniectomies for subdural empyema and infectious sinusitis; 7 separate abscesses were drained once each and did not recur. The cultured organisms varied, but half of the pathogens were anaerobic.

There was one complication of postoperative hemorrhage in a 24-year-old woman with metastatic melanoma in the right frontal lobe. Four hours after biopsy, her level of consciousness suddenly became obtunded. Follow-up CT (Fig. 4) revealed bleeding within the tumor; she expired before surgical intervention could be attempted.

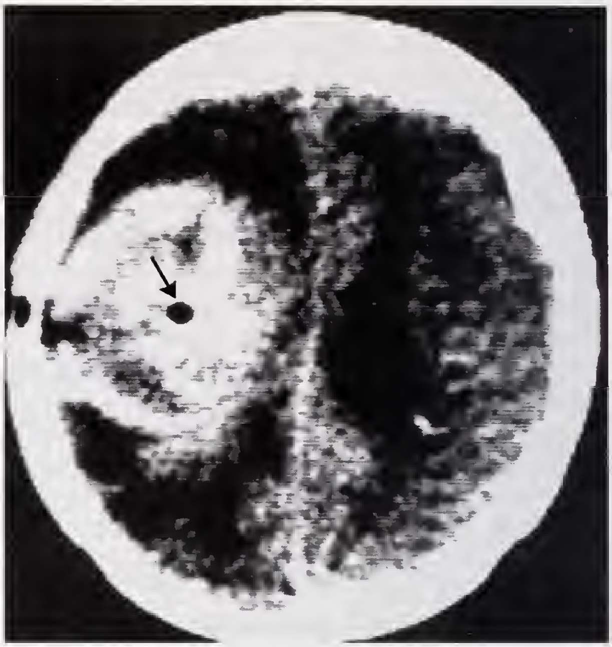

Fig. 4. Non-contrast study showing area of biopsy (air shadow — arrow) in the middle of extensive intratumoral bleeding (large white mass) with substantial midline shift.

Discussion

Seeding of a brain tumor or an abscess along the needle tract has not occurred during a one-year follow-up period. Postoperative hemorrhage resulting in operative mortality was recorded in 2 cases out of the 128 free-hand, CT-guided procedures (1.6%) previously reported in the literature (8, 13) and in 1 case out of the 201 cases (0.5%) performed with needle-stabilization devices (14). Increased intracranial pressure provides a tamponade effect to control bleeding from the needle, which was observed in 11 of my own cases but not seen at the needle tip on CT scans. Clinically insignificant hematomas were documented in several series (4, 13–15). Steroid therapy reduces the chance of neurological deterioration following manipulation of the edematous brain, but increased neurological deficits have been reported (1, 13–15). In my own series of 184 procedures, one death occurred due to postoperative hemorrhage.

A correct histologic diagnosis was made for 55 of the 60 patients with suspected brain tumors. The other 5 patients underwent open biopsy after 2 attempts 24 hours apart. Pathologists were available for frozen section at both community hospitals. Two specimens were sufficient in more than 90% of the cases. The tissue sample obtained in a 13-gauge needle was free of crush artifact on the permanent slides. Using a needle biopsy to establish the diagnosis allows most patients to choose between undergoing radiation, chemotherapy, or further cranial surgery, if necessary.

Radiologists marked the scalps of all the patients and provided depth and angulation mea-

TABLE 2
Forty Cases of Cerebral Hemorrhage (75 Procedures)

34 hypertension
4 aneurysmal bleeding
1 cerebral vasculitis
1 hypervascular neoplasm

TABLE 3
Twenty Cases of Intracranieal Abscess (42 Procedures)

17 large lesions (drained twice)
1 solitary lesion (drained once)
7 small lesions (drained once in 2 patients)

surements for needle placement. Special positioning of the head was not required in any of our cases. Although the trephine site was slightly off target in 20% of our procedures, serial CT scanning established the exact relation to the mass lesion, and the burr hole allowed for angulation of the needle.

Evacuation of hematomas due to hypertensive intracerebral hemorrhage remains somewhat controversial. If the patient has signs of increased intracranial pressure and a midline shift on CT, there is agreement that at many major medical centers neurosurgical intervention requires an extensive craniotomy. However, formal operation on the swollen hemorrhagic brain is no more likely to favorably influence the clinical outcome than one or two needle aspirations of 30–50 cc of semisolid clot (16). If the patient's blood pressure can be stabilized and there is no neurological deterioration, evacuation of a large hematoma may be expected to reduce the noxious effects of extravasated blood and hasten neurological recovery.

None of my patients with a cerebral abscess underwent craniotomy for excision or marsupialization. Aspiration of pus decompressed the brain and provided the means of identifying the organism in all of my cases. Follow-up CT studies over many months documented resolution of the lesion. The source of intracranial suppuration could be ascertained in only nine patients.

The overall morbidity and mortality (0.5%) of the methods described were quite low, due to steroid therapy, prophylactic antibiotics, and careful preparation of the access site. CT control of direct free-hand placement of needles for biopsy and drainage of intracerebral lesions compares quite favorably with more elaborate equipment (13, 14), stereotactic frames (17), and intraoperative ultrasound monitoring (18). The simple and accurate techniques presented continue to have widespread application in the practice of neurosurgery.

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Continuing Experience with Subgaleal Shunting

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Abstract

Objective: To evaluate subgaleal shunting — the diversion of cerebrospinal fluid into the subgaleal space for temporary absorption by the membranes of the scalp.
Method: Eighty-one (81) patients were treated over a 20-year period. There were 22 cases of hypertensive hydrocephalus, 52 cases of acute head trauma, and 7 cases of chronic subdural hematoma. The simple surgical technique is described.
Results: Of the eight-one patients, 33 improved, 27 did not change, and 21 expired within 72 hours. Intracranial pressure was monitored directly in 22 cases and demonstrated that subgaleal shunting provided effective short-term treatment.
Couclusious: This simple, closed method for drainage of cerebrospinal fluid avoids the complications of open ventriculostomy or open drainage of the subdural space. **Key Words:** Closed head injury, intracranial pressure, cerebral contusion, hydrocephalus, subdural hematoma.

SUBGALEAL SHUNTING was first described by von Mikulicz (1) in 1896. In 1929, Davidoff (2) reviewed the technique for the relief of hydrocephalus. Chronic postoperative cerebrospinal fluid fistulae were subsequently treated by ventriculosubcutaneous drainage (3, 4) before Perret and Graf (5) in 1977 reported a method of temporarily decompressing the ventricular system enlarged by tumors, and of treating recurrent subdural hematomas by diverting fluid into the parietal subgaleal space. Malis (7) advocated the avoidance of exteriorized tubes and receptacles to decrease the risk of infection associated with open ventriculostomy. Drabkin et al. (8) performed a series of 15 ventriculosubgaleal shunts by a frontal approach with patients with ventricular dilatation. The use of ventriculosubgaleal shunting in acute head trauma was first presented to the New York Society of Neurosurgery by Savitz in 1981 and published in 1983 (9). The purpose of this paper is to review and evaluate continuing experience with subgaleal shunting.

Materials and Methods

Hypertensive Hydrocephalus

Rapid increase in ventricular size, with evidence of periventricular lucencies (10) on computerized tomography, correlated well with increased intracranial pressure (ICP) in 7 patients with hemorrhagic intracranial tumors and 15 patients with subarachnoid and intraventricular hemorrhage (Table 1). After a regular trephine opening in the right parietal area, a ventricular catheter was passed into the lateral ventricle, and the proximal end was left in a previously dissected pouch in the subgaleal space. Accurate two-layer closure of the galea and skin was performed with fine sutures to prevent leakage (Fig. 1).

Acute Head Trauma

No direct measurement of intracranial pressure (ICP) was attempted in 30 cases (Table 2) of severe closed head injury treated over a 10-year

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TABLE 1
22 Cases of Hypertensive Hydrocephalus

	number	expired	permanent shunt	rehab center	home
Hemorrhagic tumors	7	-	3	2	5
Subarachnoid/intraventricular hemorrhage	15	8	3	4	3

TABLE 2
30 Cases of Head Trauma without ICP Monitoring

	number	expired	rehab center	home
Grade III	24	1	18	5
Grade IV	6	6	-	-

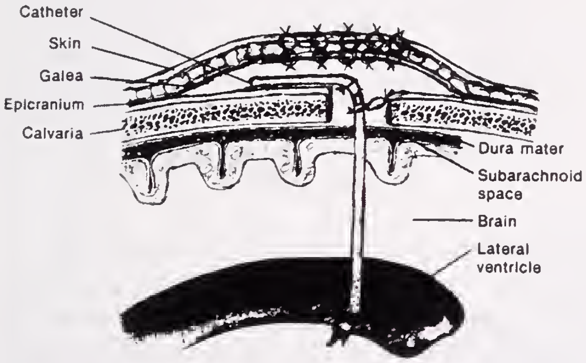

Figure. Artist's drawing of ventriculosubgaleal shunt.

period (12). All of the patients manifested signs of increased ICP and brainstem compression. Cushing's triad (bradycardia, bradypnea, and hypertension) was recorded in each case. There were no focal findings on neurologic examination and no vault fractures on skull x-rays. Dexamethasone 100 mg and 500 mL of 10% mannitol were given intravenously in the emergency room. Immediate intubation facilitated hyperventilation, and further evaluation was carried out by computerized tomography (CT) scan. Neither hematoma nor midline shift was seen in any of the patients. The ventricles were slit-like, and vesicular hemorrhage in white matter or blood in the ventricular system, or subependymal bleeding, was visualized.

The small ventricles were tapped by a right frontal approach just anterior to the coronal suture, which was made with a hand drill. The cerebrospinal fluid obtained under pressure was 10 – 20 cc in volume and grossly hemorrhagic. A Pudenz ventricular catheter was inserted, and 4 cm of tubing was tucked into an 8-cm pocket created above the periosteum by dissecting the loose areolar subgaleal tissue. Prophylactic methicillin was administered intravenously every 6 hours. When the Camino ICP monitor became available (11), the device was inserted into the left frontal subarachnoid space of 22 patients (Table 3) prior to placement of a ventriculoperitoneal shunt in the right frontal lobe. Initial Glascow Coma Scale ratings were 3 – 5. The catheter was removed after 7 days without complications.

Chronic Subdural Collections

Three patients over 50 years of age in Savitz's (10) series presented with an acutely obtunded mental status and were diagnosed as having bilateral subdural hygromas on CT. Because of cerebral atrophy, even in the presence of ventricular enlargement, there was no clear evidence of elevated ICP. Four other patients over 50 years of age, who had undergone drainage of chronic subdural hematomas by limited craniectomy and insertion of a Jackson-Pratt drain, reaccumulated fluid in the subdural space and reversed their neurologic recovery. All 7 patients (Table 4) were treated by placing a Pudenz ventricular catheter in the subdural space. When no craniectomy site was available, a single burr hole was made in the right parietal area with a hand drill. About 4 cm of tubing was tucked into an 8-cm subgaleal pocket created above the pericranium. The shunts were removed after 10 – 14 days without complications (11).

Results

Hypertensive Hydrocephalus

Eight of the 22 patients expired within 72 hours. Temporary drainage of cerebrospinal fluid

TABLE 3
22 Cases of Head Trauma with ICP Monitoring

sex	age	Glasgow Coma scale	complications	initial ICP	post shunt ICP	tracheostomy gastrostomy	outcome
F	23	4	otorrhea	25	0–5	no	home
M	19	4		31	3–10	no	rehab center
M	30	5		26	3–10	no	rehab center
M	32	3	C2 fracture	28	3–10	yes	expired (72 hours)
M	19	5	brachial pl avulsion	31	0–7	yes	rehab center
F	70	3	old left CVA	27	0–4	no	expired (72 hours)
F	44	5	ovarian carcinoma	52	0–8	yes	rehab center
F	16	4	hemothorax	29	2–10	yes	rehab center
M	16	5	rhinorrhea	28	0–8	no	rehab center
F	15	3	rhinorrhea	82	6–18*	yes	expired (72 hours)
F	29	3	otorrhea	52	2–10	no	expired (72 hours)
M	61	5		38	3–10	yes	rehab center
M	50	5		21	0–6	no	rehab center
M	30	5		32	0–8	yes	rehab center
M	22	3	otorrhea	80	4–16*	no	expired (72 hours)
M	18	5		21	2–10	no	home
F	31	5		24	0–6	no	rehab center
M	19	5		28	0–7	no	rehab center
F	17	4		30	2–10	yes	rehab center
F	63	5	otorrhea	77	5–10	no	rehab center
M	40	4		57	0–4	no	expired (72 hours)
M	16	4		40	0–9	no	rehab center

* insertion delayed due to coagulopathy
Adapted from Reference 11.

TABLE 4
7 Cases of Chronic Subdural Hematoma

	number	improved	unimproved
primary bilateral	3	1	2
secondary unilateral	4	4	-

for several weeks provided emergency decompression of the ventricular system with no syphon effect in the other 14 patients. Fibrotic processes progressively stopped the absorption after longer periods. While the subgaleal pocket was soft and fluctuant, simple palpation demonstrated that the ICP was low. If the collection became tense, the galeal and periosteal membranes were no longer able to handle the underlying uncorrected pathology. Eight of the 14 patients improved (Table 1). The shorter catheter was easily removed for insertion of a ventriculoperitoneal or ventriculoatrial shunt in 6 cases that had to be converted. There were no complications of wound infection or intraparenchymal hemorrhage.

Acute Head Trauma

In the first 30 cases shunted without a monitor (Table 2), CT evidence of compressed ventricles and cerebral contusion correlated well with increased ICP (13). Six patients categorized as grade IV (no evidence of brain function) in the emergency room did not improve and died within 72 hours. The remaining patients, categorized as grade III (no eye opening, no verbal response, motor response limited to abnormal flexion or extension), were transferred to a rehabilitation center, with the exception of one 16-year-old boy who suffered a fatal pulmonary embolus on his 30th postoperative day. Every patient was tube fed after the third day of hospitalization. In 12 cases, tracheostomy was required. Subgaleal collections of fluid lasted 3–5 days — the period of brain swelling. The reduction in ICP was revealed by immediate improvement in neurological status; hyperventilation, hypertension, and hyperthermia also resolved. Three patients with rhinorrhea stopped leaking cerebrospinal fluid from the nose after shunting.

The initial pressure was over 20 torr (normal < 10 torr) in the 22 cases that were monitored (Table 3). The recorded ICP in 19 cases remained in normal range for the 72 hours of monitoring after a single IV dose of mannitol. Three of the 6 patients who expired had required additional intravenous doses of mannitol in order to maintain the ICP below 20 torr. Eight patients required tracheostomy and gastrostomy. One patient regained normal cortical function during her hospitalization for multiple trauma. After 2–6 months of rehabilitation and occupational therapy, 15 patients were discharged home to the care of their families. Follow-up CT scans in the 6 cases who met brain death criteria within 3 days showed extensive hemorrhagic infarction rather than resolution and absorption of areas of contusion. Nine patients with basilar skull fractures ceased leaking cerebrospinal fluid after shunting.

Chronic Subdural Collections

Two of the 3 patients presenting with bilateral subdural hygromas on CT had minimal filling of the subgaleal pocket and no neurological improvement. In one patient with chronic bilateral subdural hygromas and in all 4 patients with recurrent subdural hematomas, the subgaleal collection remained tense and resolved over a 10–14 day period; signs of elevated ICP resolved in all 5 cases (Table 4).

Discussion

Perret and Graf (6) did not list any references following their article in 1977; but in a response (14) to a letter to the editor by Ferreira (15), they reviewed the prior neurosurgical literature on subgaleal shunts (1, 3–5). Malis (7), commenting on ventriculosubgaleal shunting and ventriculostomy infections in a paper by Hollaway et al. (16), stated that open drainage was consistently avoided at The Mount Sinai Hospital. This practice had been taught by Professor Jean Michel Gybels of Belgium (17). Hollaway et al. (18), in their response, recognized the advantage of a closed system for ventricular drainage in order to avoid infection, but raised the question of efficacy and the potential for back pressure once the subgaleal pocket had filled.

The absorptive capacity of the subgaleal space has been well documented (3, 6, 8). Inasmuch as high-pressure hydrocephalus was controlled for periods of from 3 weeks up to several months in our series, the membranes of the scalp must have contributed to handling the high volume of cerebrospinal fluid that reduced pressure to normal range. In other patients, with intracranial hematomas, midline shifts, and extensive cerebral contusion, leakage into the subgaleal space following decompressive craniectomy could not decrease elevated ICP, even with hypnotics, hyperventilation (hypocarbia), hypothermia, and intermittent mannitol. Which of many factors, such as normal circulation, choroid plexus formation, transependymal absorption, arachnoid villus transport, and elastance and compliance of the brain, influence cerebrospinal fluid perfusion has not been determined (19).

While attempts to cannulate slit-like ventricles may produce intracerebral bleeding, no postoperative hemorrhages due to shunt placement were seen on follow-up CT scans. The shunts were removed after one week to avoid formation of a subdural hygroma; tracking of fluid around the tubing may occur with or without obstruction of catheters left in place (8, 14, 20). Successful treatment of cerebrospinal fluid fistulae by indirect shunting rather than direct repair has been documented in the neurosurgical literature (4, 5).

In the cases requiring shunting of the subdural space, persistence of the subgaleal collection for up to 10–14 days was consistent with increased ICP, while early resolution was diagnostic of a preexisting hygroma. Avoidance of open drains eliminated the sequela of tension pneumocephalus. Perret and Graf (6) described multiple taps of the subgaleal pocket for diagnostic and therapeutic purposes. Absorption and resolution in the 7 patients with chronic subdural collections were monitored only by serial CT scans (11).

Conclusion

Ventriculosubgaleal shunting can act as a safety valve for continuous reduction of elevated ICP in closed head injuries. The subgaleal space is able to provide adequate drainage and absorption of cerebrospinal fluid during the period of traumatic brain swelling. Insertion and removal of catheters may be performed rapidly using minimal anesthesia. Avoidance of the exteriorized tubes and receptacles inherent in more elaborate methods of treating increased ICP lowers the risk of infection and facilitates intensive nursing care of comatose patients. Certainly, ICP monitoring over a 72-hour period lends credence to the efficacy of such shunting. The simple method of employing the membranes of the scalp for the temporary relief of elevated ICP has widespread application in acute head trauma, hypertensive hydrocephalus, and chronic subdural collections.

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The Evolution of Percutaneous Spinal Endoscopy and Discectomy:

State of the Art

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Abstract

Objective: The author relates his 7 years' experience with endoscopic spine surgery for lumbar disc herniations and conditions previously treated only with more invasive methods.

Materials and Methods: Five hundred (500) patients were treated with the Yeung endoscopic spine system, which features an endoscope with a 2.8 mm operating channel. The protocol included preoperative or intraoperative discography in all cases. Adjuvant therapies were employed in various clinical conditions when dictated by the visualized spinal pathology — KTP laser (Laserscope, San Jose, CA) in 100 patients, radiofrequency by electrothermal probe in 400 patients, chymopapain in 50 cases, and intraoperative steroids in 100 cases. A newer slotted tube system allowed for foraminoplasty and removal of osteophytes or extruded fragments.

Results: Good-to-excellent results were recorded in 432 of the 500 patients (86.4%). Separate analysis was made of the first 100 cases when the KTP laser was in use.

Conclusions: The 2.8 mm operating channel scope produced clear visualization of annular tears, disc fragments, foraminal osteophytes, and the epidural space. Monitoring of the microinstruments in the disc space and spinal canal was readily accomplished. The quality of the imaging provided by discography improved the definition of the disc pathology. Adjuvant use of lasers, radiofrequency, chymopapain, and intradiscal steroids and the newer slotted tube system, have contributed to the advances in minimally invasive technique for endoscopic discectomy. **Key Words:** Herniated lumbar disc, endoscopic discectomy, chymopapain, radiofrequency, discography, inflammatory membrane, thermal modulation, annular tear.

Introduction

BEFORE THE ADVENT OF percutaneous techniques, the only surgical treatment for herniated lumbar discs was posteromedial laminectomy, or laminotomy and discectomy. In an attempt to decrease surgical morbidity, the microscope was employed in conjunction with smaller incisions to minimize operative trauma to the bone and soft tissue. The earliest percutaneous methods concentrated on lateral approaches to the intervertebral disc and avoided breaching the spinal canal. With endoscopy came the ability to observe the disc space pathology, monitor removal of nucleus pulposus, and control adjuvants such as laser and radiofrequency. Nevertheless, a number of problems arose, including the need for expensive, nondisposable endoscopes and lack of size standardization. With smaller and disposable flexible endoscopes and equipment, visualization of the nerve root was enhanced. Thereafter, specialized instruments were developed to perform foraminoplasty and remove osteophytes.

Materials and Methods

Yeung Endoscopic Spine System (YESS)

Five hundred patients were treated by the author between November 1991 and December 1998. Most of the cases had a variety of symptomatic disc protrusions, including recurrent, extruded, migrated, and sequestered disc fragments within reach of the YESS instruments. A subgroup with discogenic back pain due to annular tears was studied prospectively. In this group, selective endoscopic discectomy was combined with thermal discoplasty as an alternative to fusion.

Every patient underwent targeted endoscopic discectomy. Even when there was extruded foraminal and extraforaminal disc tissue in the path of the operative cannula, the "inside-out

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technique" decompressed the disc and created a working cavity within the disc. With this staging area accomplished, the visualized pathology was addressed, aided by adjuvant therapy.

This third-generation of instruments featured reusable, durable equipment. Multichannel inflow and outflow ports allowed suction through the working port and provided quality imaging (Fig. 1). The posterolateral portal was bordered by the superior facet of the inferior vertebra dorsally, the exiting nerve root ventrally, and the superior end plate of the inferior vertebra caudally (Fig. 2). The slotted cannula system protected neural tissue while allowing access to the pedicle and facet (Fig. 3A). Foraminoplasty was possible with trephines, rasps, burrs, and use of the laser (Figs. 3B and 3C).

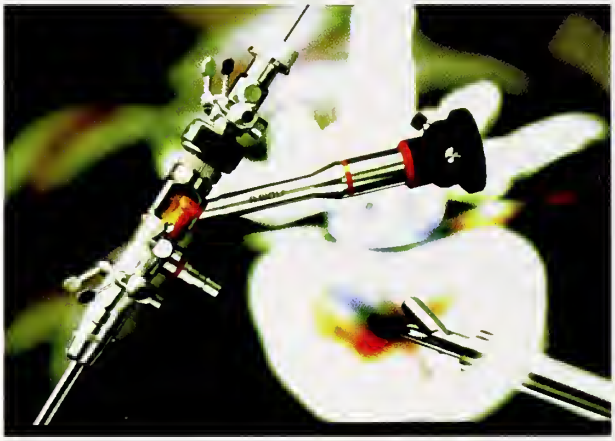

Fig. 1. Illustration of YESS endoscope with multichannel inflow and outflow ports, and forceps extending through distal end.

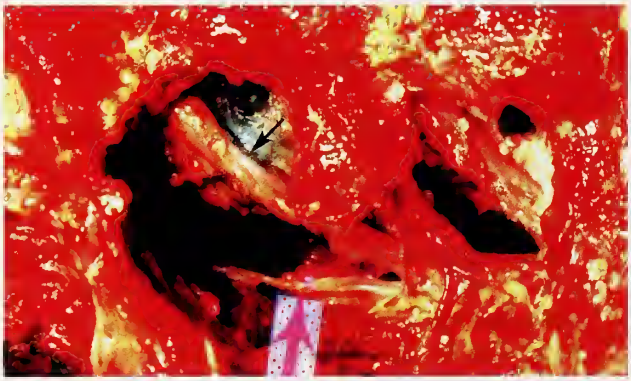

Fig. 2. The femoral-genital nerve (red arrow), found along the psoas muscle is in close proximity to the exiting nerve root (black arrow).

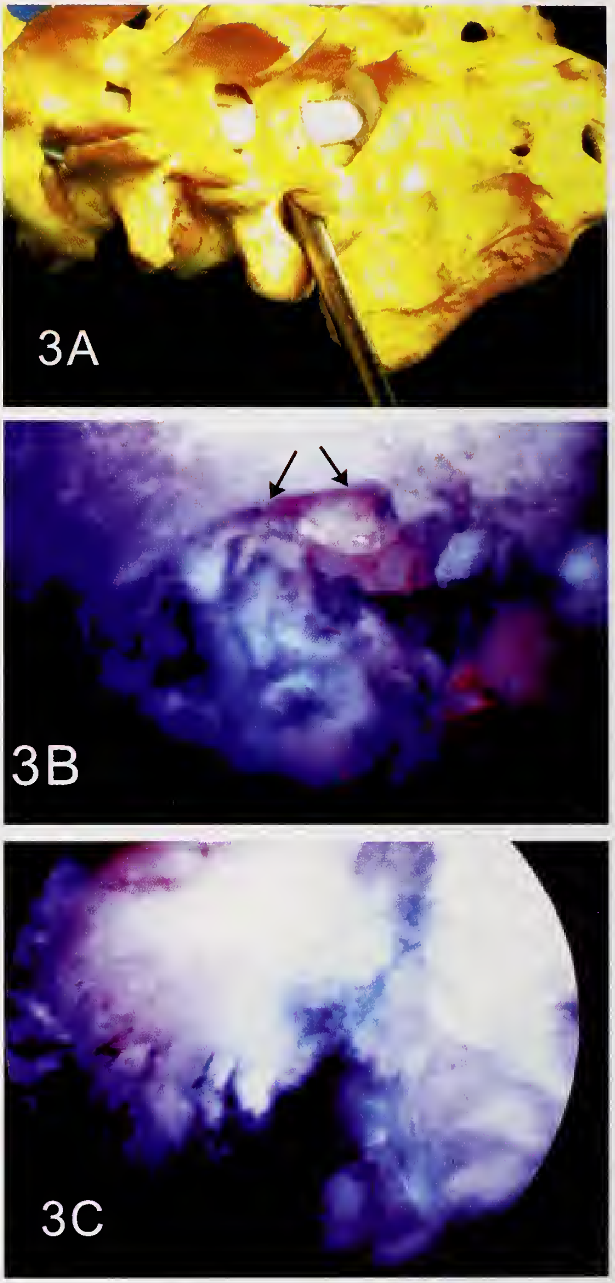

Fig. 3 **(A)** Slotted cannula placed under the superior facet of S1. **(B)** Superior facet (arrows) after foraminal enlargement at L5–S1. **(C)** Note absence of facet removed as part of foraminoplasty to relieve lateral recess stenosis.

Discography

Indigocarmine dye 1 cc was mixed with 4 cc of iopamidol 41% and injected into the nucleus pulposus. Degenerative structures within the disc were stained. Normal disc tissue was firm and resilient, would not stain, and could easily be distinguished from the "crab meat" consistency of abnormal nucleus pulposus (Fig. 4). The presence or absence of leg pain (visual analog scale 1 – 10) and the endoscopic findings were correlated with the preoperative MRI on an Image Manager, a computer database, which prepared a comprehensive report including the intraoperative

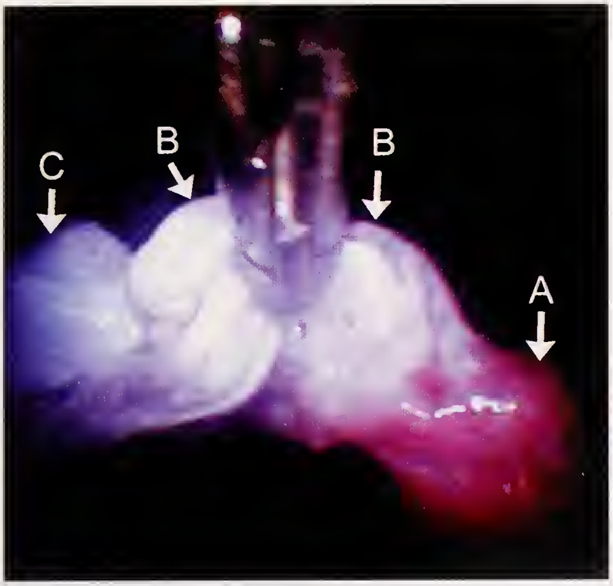

Fig. 4. Herniated disc fragment. Note inflamed portion **(A)** in epidural space, white portion **(B)** trapped in annular defect, and blue-stained portion **(C)** within the disc.

discogram and the endoscopic findings (Table 1). Only posterior tears are detected by MRI. Lateral tears are visualized by discography (Fig. 5) and usually produce groin and thigh pain. If localized to one or two quadrants, thermal contraction produces healing within 3 – 6 months. Extensive tears are more often associated with degenerative spondylolisthesis and require interbody fusion.

The severity and grading of annular tears are described in Table 1. Grades I and II never produce pain. Grade III radial tears produce pain at moderate pressures. MRI findings of a high intensity zone in the posterior annulus correlated with Grade IV and V tears, and were associated with non-dermatomal pain. Grade V tears (Fig. 6) were often associated with an inflammatory membrane which spread beyond the area of tear. Far lateral and ventral tears were readily visualized endoscopically and were often associated with soft nucleus pulposus interposed between the collagen bundles of the annulus.

TABLE 1
Grading of Annular Tears
(Modified Dallas Discogram Description)

Grade I	normal cotton ball pattern no extension beyond central half of disc
Grade II	normal lobular pattern no extension beyond central half of disc
Grade III	fissured extension to inner annulus no disc protrusion
Grade IV	degeneration + extension to outer annulus may include disc protrusion
Grade V	degeneration past annular extension definite protrusion + possible extruded fragment

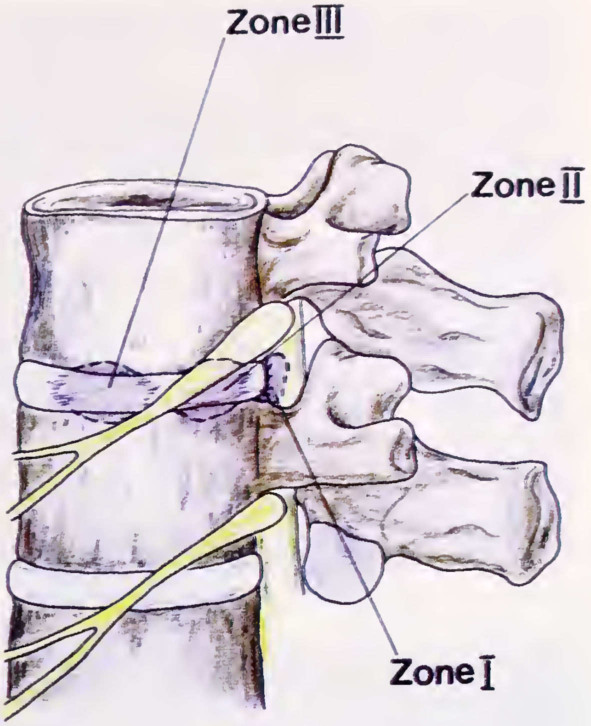

Fig. 5. Three zones of annular tear and disc protrusion. Zone I posterior tears are detected by MRI. Zone II tears directly involve the exiting nerve root. Zone III tears are best detected by evocative discography.

KTP Laser

The first 100 cases, in which the KTP laser (Trimedyne, Irvine, CA) was employed for disc decompression and ablation, were previously reported (1). The laser aided visualization by clearing the cavity of residual disc material not completely removed by instruments. Hemostasis was provided by thermocoagulation.

Chymopapain

Low dose chymopapain (500 units) was used as adjuvant therapy in 50 cases of large herniations, where the configuration of the herniation indicated possible difficulty with mechanical removal of the disc from the inside. Chymopapain was incorporated when a review of the technical failures included retained fragments that

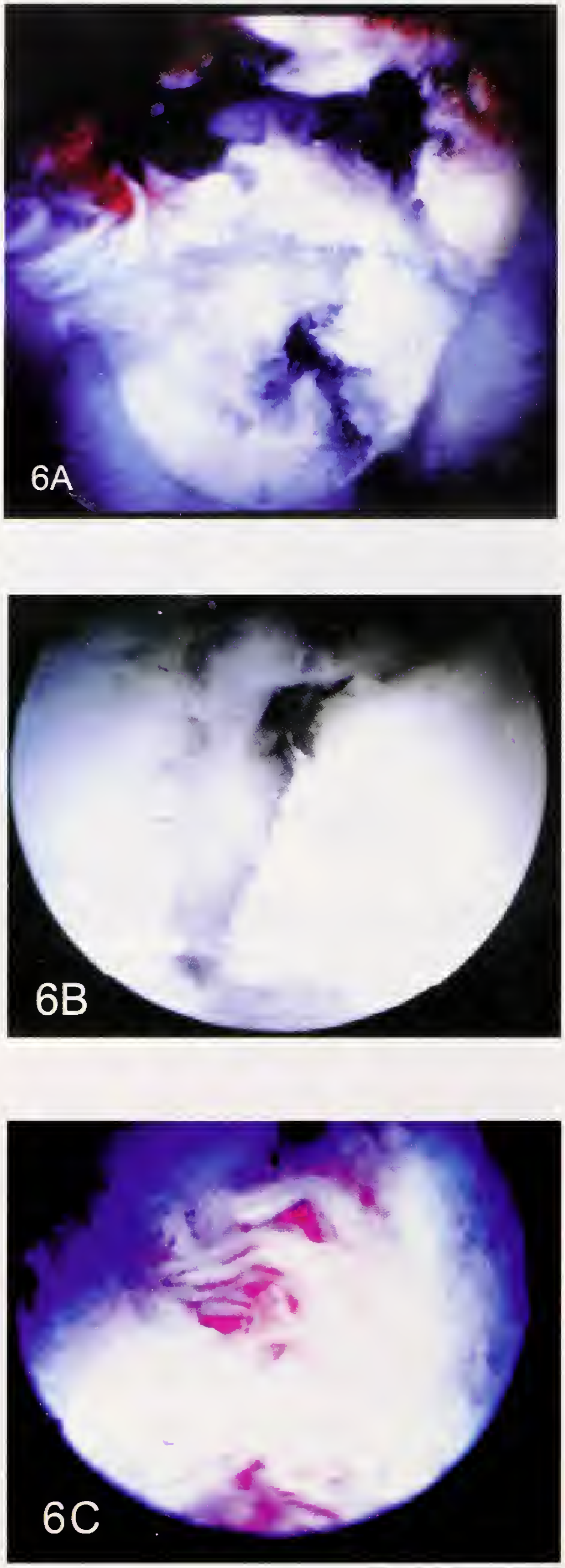

Fig. 6. Grade V annular tears. **(A)** Herniation extending into epidural space. **(B)** Interpositional disc fragment. **(C)** Note repair following thermal contraction.

separated from the main body of the herniation during extraction from within the disc. When disc fragments were found to be extruded and migrated behind the vertebral body or when there was a recurrent herniation, chymopapain was used to decrease the recurrence rate and dissolve the missed fragments. The patients all received cimetidine 100 mg and diphenhydramine 50 mg intravenously preoperatively. The chymopapain was injected and left in the nucleus pulposus for 5 – 10 minutes before fenestration of the annulus. There were no adverse reactions. When iopamidol was employed, if the contrast material was immediately absorbed into the bloodstream or entered the thecal sac, chymopapain was not injected.

Radiofrequency

In the remaining 400 cases, a radiofrequency electrode (Ellman International, Hewlett, NY) was substituted for the KTP laser. The probe was highly satisfactory for coagulating small bleeding vessels, and causing the annulus and disc material to contract. After thermal contraction, loosened soft and collagenized disc tissue was removed with manual instruments and motorized suction devices. The radiofrequency device has evolved from a straight electrode to a flexible, steerable probe with a thermal couple for temperature control.

In patients without disc protrusion but with painful Grade III + IV (Table 1) annular tears, nucleus pulposus may be observed as interpositional material between the collagen bundles and may be responsible for the tear not healing. More recently, when granulation tissue or an inflammatory membrane has been identified adjacent to grade V tears that extend to the epidural space and outer annulus, ablation has been accomplished with an electrothermal probe (Oratec Interventions, Inc., Menlo Park, CA). The annular tissue contracts with the use of the unipolar, flexible, temperature-modulated instrument, and the herniation defect is effectively closed.

Intraoperative Steroids

In 100 patients, whenever an inflammatory membrane was observed in the annulus, stimulation of the nerve and surrounding tissue elicited pain. Even when a foraminal herniation was encountered, the annulus was dilated at the base of the herniation and the fragment was pulled back into the disc space before being extracted — “inside-out technique” (Fig. 7). Depo-Medrol 80 mg in 1 cc of saline was placed intradiscally at the conclusion of the discectomy.

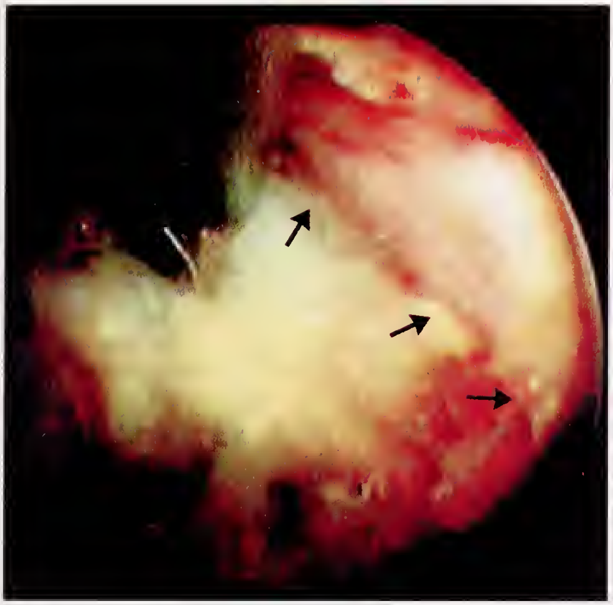

Fig. 7. Foraminal herniation (arrows) against traversing L5 nerve root.

Results

Good-to-excellent results were recorded in 432 out of 480 cases (90%); 20 patients were lost to follow-up. Of the first 100 operations, in which the KTP laser was employed, 80 patients (Table 2) were available for evaluation; good-to-excellent results were noted in 56 cases (70%) and fair-to-poor results in 24 (30%). The mean age was 42 years, with a range of 25–69 years. Good-to-excellent results occurred in 24 of the 32 patients (80%) presenting with predominant leg pain, but in only 30 of the 48 patients (63%) with pain confined to the low back. Eight patients (10%) who did not improve underwent successful open discectomy; the findings at surgery were either an extruded fragment or unrecognized foraminal stenosis.

In order to evaluate the electrothermal probe, the next 50 consecutive patients were reviewed. Forty-five cases (90%) reported pain relief. Grade III tears involving less than one-half of the dorsal annulus responded best, with pain relief occurring between one week and 3 months after the procedure. Grade IV tears involving 50% or more of the annulus took an average of 3–6 months for back-pain relief, while Grade V tears took up to 9 months for improvement. In another preliminary prospective study of 50 patients, good-to-excellent results were recorded in 42 cases (84%).

TABLE 2

80 out of 100 Patients in Follow-up Study

Level	Patients
L2–3	2
L3–4	12
L4–5	28
L5–S1	21
L4–5 + L5–S1	17

The clinical results were rated by a combination of modified MacNab criteria and Adam's classification (2). The extent of the tear was determined by a modification of the Dallas Discogram Description (3). The tear pattern was further divided into radial and circumferential components as per Osti et al. (4). The overall purpose was to record discogram patterns and radial extension into the peripheral annular fibers, by the number of quadrants involved, but not depend on CT scan findings to rate the tear.

Complications were limited to temporary dysesthesia in 20% of patients. The cause was thermal irritation of the traversing nerve root or dorsal root ganglion. The heat of thermocoagulation may have spread through annular fissures or defects. More recent modifications in the radiofrequency probe allow for constant irrigation with cold saline. Continuing paresthesias and quadriceps atrophy occurred in two patients.

Discussion

In 1963, Lyman Smith (5) reported the effects of chymopapain on symptomatic disc herniations. The enzymatic debulking of the nucleus pulposus was validated by two large double-blind studies and a number of cohort studies (6–8). However, chymopapain was not as effective on hard collagenized fragments or sequestered and migrated fragments (9, 10). With the use of 2,000 units, systemic reactions due to vascular dispersion and injection outside the nucleus pulposus were associated with transverse myelitis and other unacceptable complications (11). Employing lower dosages (500 units) softened collagenized fragments and made extraction easier. When chymopapain was not injected, the electrothermal probe produced contraction of the annular fibers and dislodged fragments trapped in the annulus.

The intraoperative discogram has become an essential test during spinal endoscopy to confirm the pathology seen on preoperative imaging studies. The vital dye can fill the herniation defect, target degenerative material, warn the surgeon of non-containment if contrast extravasates, or simply outline the annular defect for thermal shrinkage. Classic extruded disc herniations are usually caused by collagenized fragments that are trapped by the annulus and cannot retract back into the disc space. Herniations are often seen as a void on the discogram, as opposed to contrast material filling the protrusion. Extracted fragments can be examined in previously unappreciated detail.

Hijikata (12) and Kambin (13, 14) developed the mechanical and endoscopic approach to the lumbar disc in the early 1970s. Kambin (15) and Craig (16) refined their systems to allow for targeted fragmentectomy by uniportal and biportal techniques. Craig-type cannulas (16) were employed with manual and automated instruments to remove disc tissue from the triangular working zone between the traversing and exiting nerve roots. Initially, one cannula size and configuration allowed limited irrigation exploration. Later development of an oval cannula allowed fanning of instruments more dorsally and ventrally. When coupled with rigid patient selection, the reported surgical outcomes were comparable to those of open laminectomy (87% good-to-excellent results) (17, 18).

Without adequate evaluation of the epidural space by preoperative imaging studies, small extruded fragments and lateral recess stenosis could not be consistently ruled out and were the reported causes for clinical failure. Annular tears in the ventral and far lateral zone of the disc seen by intraoperative discography were often missed by MRI.

With newer slotted tube systems, it is now possible to remove bone, perform foraminoplasty, and excise extraligamentous disc fragments (19). Special cannulas have also been designed for inserting spinal implants and enlarging the subarticular recess. Depending on the location and size of the herniation, a uniportal or biportal technique can be used for posterolateral fragmentectomy. With the ability to visualize the spinal anatomy in a conscious patient comes the opportunity to diagnose, evaluate, and treat painful conditions that are still poorly understood.

Summary

Minimally invasive techniques offers an alternative to both conservative therapy and open surgical treatment of discogenic pain. The state of the art in percutaneous discectomy is no longer limited to contained disc herniations. Surgeons can now remove extruded and migrated fragments as long as they can reach the pathology involved. YESS gives access to the epidural space from pedicle to pedicle at each lumbar level. Development of instrumentation continues apace, with application of adjunct therapies such as discography, electrothermal probes, low dosages of chymopapain, and intradiscal injection of steroids. Future studies are needed to evaluate prosthetic disc replacement, and tissue responsiveness and healing.

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Supraorbital Burr Hole Via a Glabellar Incision:

A Simple Approach to Anterior Skull Base

GIDEON ZUCKER, M.D., AVI COHEN, M.D., EMANUELA CAGNANO, M.D., AND ELI REICHENTHAL, M.D.

Abstract

A left subfrontopolar lesion with marked edema was totally resected utilizing a minimally invasive approach. It was possible to expose and resect the lesion, which turned out to be a tuberculoma, through a burr hole placed supraorbitally through a glabellar incision. The development and significance of minimalization techniques for surgery in the skull base region are discussed.

Key Words: Minimally invasive surgery, burr hole, skull base, tuberculoma.

PREVIOUS TECHNIQUES for removing skull base lesions necessitated excessive brain retraction, causing edema and neural damage. In the last two decades, surgical approaches to the skull base have undergone a dramatic modification, with the adoption of more extensive bony resection. These approaches, which are state of the art at present, have decreased cerebral damage by minimizing brain retraction. However, they are complicated and too extensive in opening and closure, time consuming, and associated with increasing morbidity. Although recent experience has led to simplified opening and closure, it is understood that a minimal opening with sufficient exposure would serve the same purpose, with shorter operative time and lower morbidity.

Case Report

A 57-year-old woman who emigrated to Israel from India was in generally good health. When first seen, she suffered from a subcutaneous neck abscess, which was drained in an outpatient clinic, with no further consequences.

One month later, the patient was admitted to the hospital following loss of consciousness, generalized seizures and right-sided weakness.

Neurologically she was comatose, and had a right-sided weakness and a right-sided central facial palsy; no papilledema was demonstrable on funduscopic examination. The general physical examination was unremarkable.

Biochemical and hematological blood tests, including blood count and blood cultures, were normal. An urgent brain CT, with and without contrast enhancement, demonstrated a space-occupying lesion at the left anterior skull base lateral to the crista gali. Contrast media enhanced the lesion, which was surrounded by a large edematous area (Fig. 1A). The patient was thought to have a cerebral pyogenic abscess; she was started on anticonvulsants, steroids and antibiotics. CT performed one and four days following admission did not show any change in the lesion.

Several days after admission, due to the lack of clinical and radiological improvement, the patient was taken to the operating room. Under general anesthesia, a left glabellar incision was performed, extending from 2 cm medial and 1 cm lateral to the supraorbital notch (Fig. 2A). The supraorbital nerve was preserved. A burr hole

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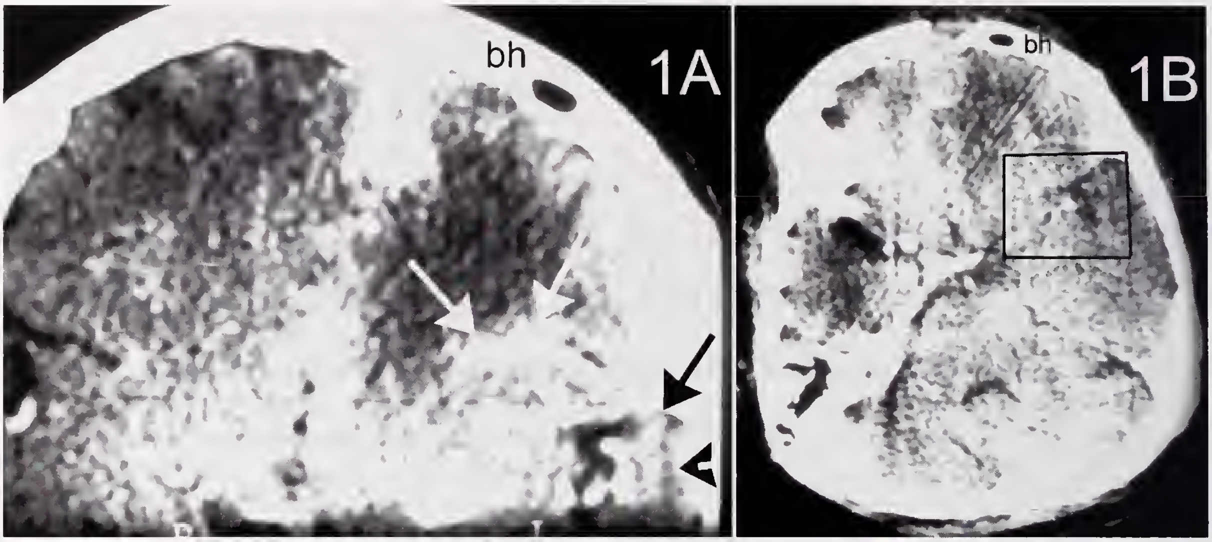

Fig. 1. **(A)** CT of the brain with intravenous contrast, revealing an enhancing left subfrontopolar lesion adjacent to the crista gali (black arrow and arrowhead) and surrounded by edema (white arrows). Burr hole is indicated by bh. **(B)** Repeat CT one day following the operation. A complete resection of the lesion is evident. The indicated rectangle is the area in which the resection was performed.

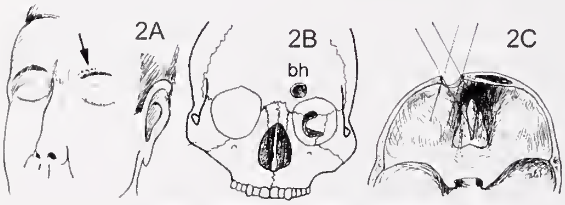

Fig. 2. **(A)** Schematic diagram of the placement of the glabellar incision (arrow). **(B)** Schematic drawing of the burr hole (bh) placement. **(C)** Schematic drawing of the angles accessible for surgical exposure.

was drilled under the operative microscope, 1 cm lateral to the midline and medial to the supraorbital notch and 1 cm above the orbital rim (Figs. 2B and 2C). Following dural opening, the lesion, which was located at the pole of the frontal lobe, was identified and excised. Marked post-excisional bleeding was easily controlled. The wound was closed with gel-foam and the skin was sutured in two layers. The operative time was 40 minutes.

One day following the operation, a CT scan with and without contrast media disclosed complete removal of the lesion (Fig. 1B).

Postoperatively, there was an immediate improvement: the patient was alert, seizures had ceased and the hemiparesis had disappeared. Histopathological examination disclosed a necrotizing, granulomatous reaction with extensive caseous necrosis in which numerous giant cells of Langhans were seen suggestive of a tuberculous abscess (Fig. 3). The patient was started on antituberculous medication.

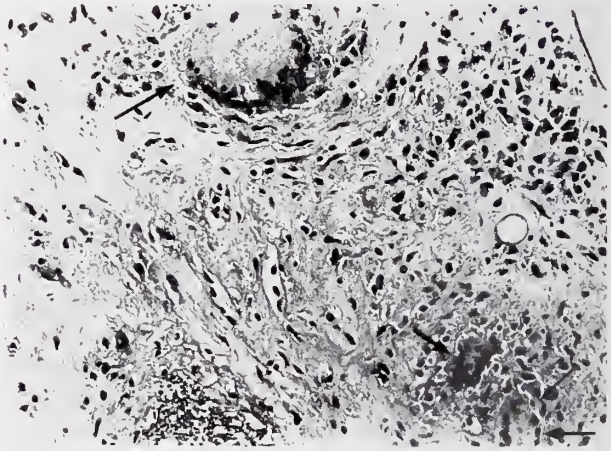

Fig. 3. Microscopic section of the resected tumor (H&E, 40x), showing granulomatous reaction with mononuclear cell infiltrate and three Langhans' giant cells (arrows) with typical nuclear horseshoe pattern.

Discussion

Our reported case clearly demonstrates the advantage of using a simplified approach rather than performing "classical" craniotomy. Previously, this patient would have undergone a relatively large frontal craniotomy and frontal lobe retraction in order to expose the lesion at the base of the skull. Brain retraction would have induced further brain damage and edema, thus increasing morbidity.

In order to prevent retraction-induced brain injury for lesions located at the base of the skull, various approaches have been developed. Improvements in technique have led to smaller surgical field exposures.

Derome (1), Dolence (2), Sekhar et al. (3), and Hakuba et al. (4) advocated the innovative extensive exposure to lesions at the base of the skull, starting with extensive skin incisions, bone resection and brain exposure. All of these solved the problem of brain retraction. However, the operative field itself remained small.

The trend now is to get to the same working operative field with less-extensive openings. This has resulted in the development of approaches which permit decreasing the extent of the surgical exposure. Recently, Perneczky (5, 6) described a minimally invasive approach known as the key-hole craniotomy. With this approach, the size of the surgical exposure is 2 cm in diameter. Thus, the opening must allow for sufficient intracranial space and an overlapping exposure and operative field, so that the lesion can be excised with minimal trauma to the surrounding brain.

Jho (7) described the excision of subfrontal and suprasellar lesions through an orbital craniotomy via an eyebrow incision. This method is a further minimalization of the supraorbital approach described by Jane (8). This procedure, however, can be utilized only in a select number of cases, where the lesion is close to the surface, small in size and subfrontally located.

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Dermatology Notes

Herpes Zoster

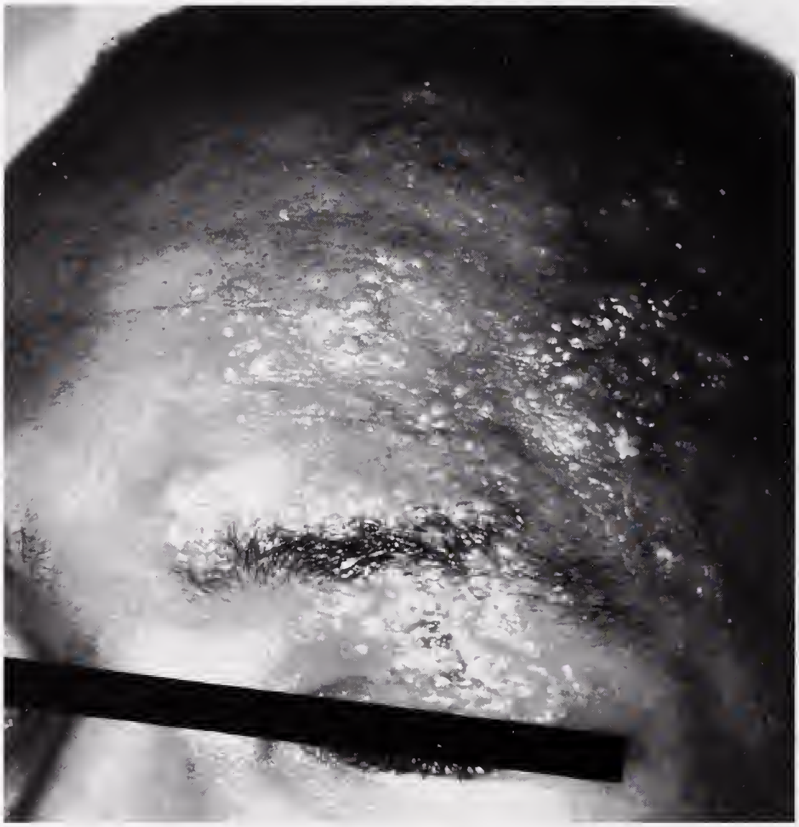

Fig 1. Herpes zoster in a 32-year-old HIV$^+$ patient. Grouped vesicles on an erythematous base are seen in the distribution of the first division of the trigeminal nerve. Note that the lesions do not cross the midline.

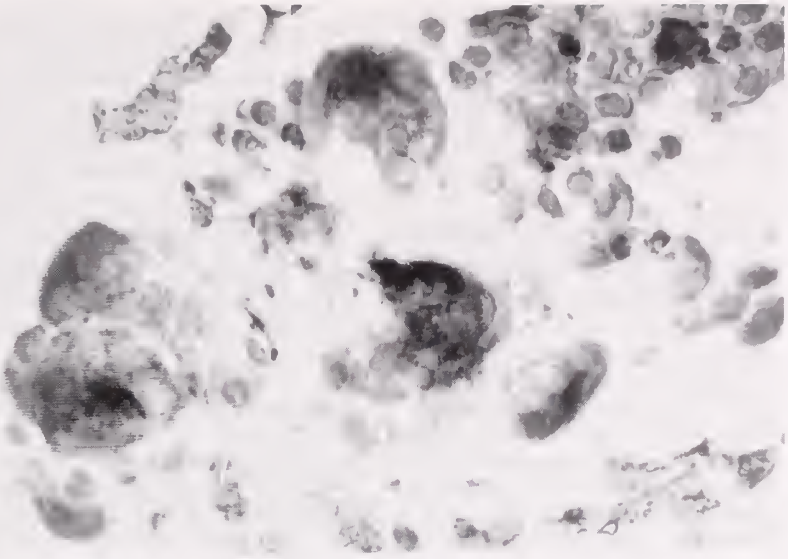

Fig 2. Tzanck smear demonstrates several multinucleated giant cells, a characteristic finding in herpes infections. Although not specific for herpes zoster, it confirms the diagnosis in the proper clinical context. (Giemsa stain, original magnification 40x)

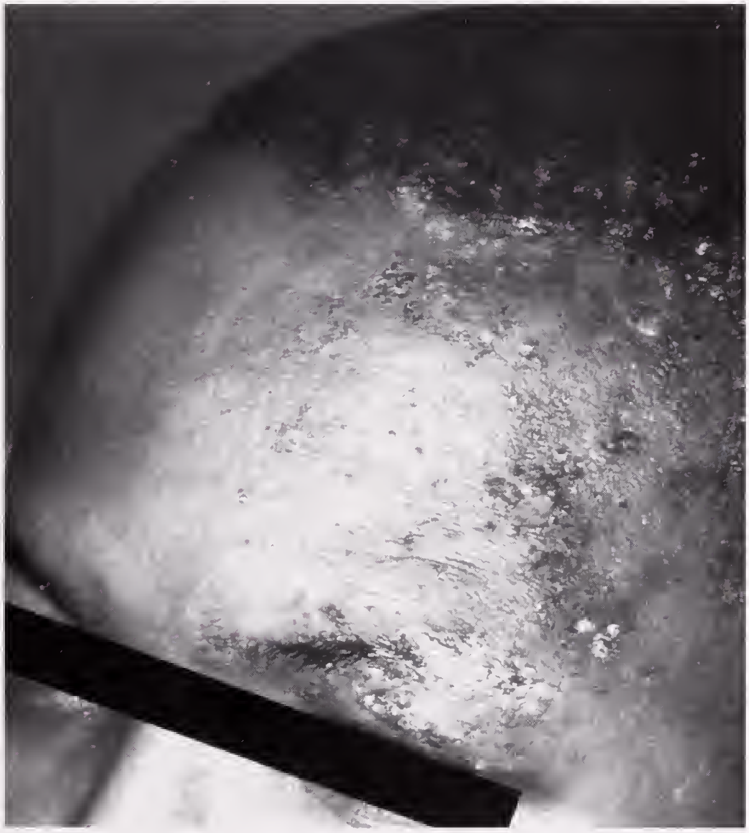

Fig 3. Same patient after three days of intravenous acyclovir therapy. Significant improvement is manifested by crusting and drying of the lesions.

THE PATIENT, a 32-year-old HIV$^+$ African-American male, presented with grouped vesicles on an erythematous base in the distribution of the first division of the trigeminal nerve (Fig.1). A Giemsa stain was performed on a scraping from the base of a vesicle (Tzanck preparation); it demonstrated multinucleated and giant epidermal cells (Fig.2). The direct fluorescent antibody (DFA) test detected varicella-zoster virus antigen, confirming the diagnosis. Most of the vesicles had crusted and dried after only three days of treatment with intravenous acyclovir (Fig.3).

Herpes zoster (HZ) represents the reactivation of a previous varicella-zoster virus infection. Characterized by unilateral pain or burning sensation, a vesicular or bullous eruption is limited to the dermatome(s) innervated by the corresponding sensory ganglion(s). In the immunocompromised host, lesions occur with increased frequency and severity and are more likely to be multidermatomal, recurrent or chronic. The latter form is seen almost exclusively in HIV$^+$ patients, in whom thickly crusted, hyperkeratotic, ulcerated lesions may be closely grouped or disseminated.

—Allen N. Sapadin, M.D. and Donald Rudikoff, M.D.

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THEME ISSUE
METHADONE SYMPOSIUM

Herman Joseph, guest editor

PART 1

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Dedication

Marie E. Nyswander, M.D. (1919-1986)

THIS ISSUE OF *The Mount Sinai Journal of Medicine* is dedicated to the memory of Dr. Marie E. Nyswander. She worked as a psychiatrist treating heroin addicts, first at the U.S. Public Health Hospital in Lexington, Kentucky and then at an East Harlem storefront and the Musicians Clinic in New York City. Her experiences formed the basis for her book, *The Drug Addict as a Patient* (Grune and Stratton, 1956). Her work at The Rockefeller University, with her husband Dr. Vincent P. Dole, led to the development of methadone maintenance and ushered in the era of treatment of heroin addicts as patients.

Herman Joseph, Ph.D.
Guest Editor

An Overview of Heroin Trends in New York City:

Past, Present and Future

Blanche Frank, Ph.D.

Abstract

Heroin abuse has been a long-standing problem in the United States, especially in New York City, which is a major heroin trafficking center and home to the largest population of heroin addicts in the country. As a consequence, New York City is also the major center for methadone treatment. Over time, however, the heroin problem seems to have changed in terms of demographic characteristics of abusers, as well as heroin purity, its associated health consequences, modes of use, and other drug patterns. Past and present heroin-involved events for New York City are examined, with some projection about the future of the heroin problem.

To identify these changes, a variety of indirect indicators of heroin abuse are analyzed. These indirect indicators include admissions to New York City heroin treatment programs, as well as heroin-involved deaths, arrests and emergency room episodes, and heroin purity levels. Additionally, a recent study of heroin abusers in New York City yielded patterns of heroin use and estimates of heroin prevalence.

The salient results indicate that, over time, Hispanics have become the predominant user group, the population of abusers is an aging cohort, heroin purity levels have risen dramatically, and intranasal use has become more prominent than injecting.

The findings have important consequences for prevention, treatment, and programs that target special populations.

Key Words: Heroin trends, heroin prevalence, epidemiology of heroin abuse, New York City heroin problem.

Introduction

New York City has long been the major center of heroin activity in the United States, and what happens here has consequences far beyond its boundaries. This paper presents an overview of New York City's heroin trends, underscoring notable changes over time — changes in the demographic characteristics of users, in the source, quality and availability of street-level heroin, and in the modes of use, as well as the health consequences associated with heroin addiction. In tracing the trends, three time perspectives are addressed: the historic past, prior to the 1970s; the recent past, the 1970s through the 1990s; and the future.

The Historic Past

According to historic analysis, opium smoking preceded heroin use, especially in New York City (1). Most narcotic abusers in the United States were women who were addicted to morphine or patent medicines containing opium. With the immigration of Chinese laborers in the mid-nineteenth century, opium smoking became a more visible form of narcotic use and spread to others in the larger community, especially artists, writers, and actors, as well as criminals.

The widening market also spurred the smuggling of opium into the country. Opium smoking, however, was perceived by the general society as a vice, leading to corruption, crime and depravity. As a consequence, in 1909, federal legislation banned the importation of prepared opium; this in turn reduced the opium supply for smoking. This decrease in availability led many who had previously smoked opium to inject morphine or heroin, a morphine derivative which had the advantages of being less bulky than opium and easily smuggled into the country. Injecting illicit narcotic

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drugs became even more widespread with the passage in 1914 of the Harrison Narcotic Act, which prevented the sale of morphine and heroin for nonmedical use.

By the 1930s, criminal organizations controlled heroin trafficking. A major consequence of this was that injection became the prominent mode of use. Since heroin was soluble and could be adulterated, and since the profit motive was obviously very strong and quality control minimal, it was most efficient and economical for the narcotic supplier to provide low-quality heroin for injection.

Helpern and Rho (2) identify the years between the end of World War I and the beginning of World War II as the period when this major change in the way narcotic addicts used drugs really took hold. The authors believe that the practice of using heroin intravenously originated in Cairo, Egypt, and spread to visiting seamen, who then introduced the practice in their ports of call (3). An important aspect of this use was the indiscriminate sharing of unsterilized syringes for intravenous injection of drugs. As a result, infections spread easily among users. Fatalities were often due to malaria, bacterial endocarditis, septic thrombophlebitis and viral hepatitis. Interestingly, quinine was used as a diluent in heroin during the 1930s. Addicts and those in the heroin trade quickly realized that quinine was a cure for and prophylaxis against malaria. Quinine as a diluent solved the problem of transmitting malaria among addicts sharing paraphernalia for injecting drugs.

The period after World War II saw an escalation in narcotic addiction. Restrictions in international travel and commerce were lifted, and criminal organizations resumed the smuggling and trafficking of heroin. Helpern and Rho, physicians with New York City's Office of the Chief Medical Examiner, and keen observers of the narcotic addict's street scene, wrote (2): "Diluted heroin mixtures sold to addicts by 'pushers' are dispensed in glassine envelopes, containing 0.2 to 0.3 gm of diluted drug of which about 18% is heroin. There is considerable variation in the total weight and strength of samples."

Thus, the stage was set for an extreme form of drug addiction in New York City, with severe health consequences. Table 1 summarizes demographic characteristics from several data sets over a 39-year period. The data for 1950 through 1967 are especially informative. First, data for 1,586 fatalities due to narcotism — mainly, chronic or acute intravenous narcotism — are presented for a period of 12 years. Clearly, the vast majority of the decedents were male (78%); more than half were black (57%), followed by whites (29%) and Hispanics (14%); and the median age was about 27 years.

Table 1 also presents the demographic characteristics of individuals who were reported to the New York City Health Department's Narcotics Register. The Register, active from 1963 to 1974, was mandated by the City Health Code to collect records of known or suspected addicts. More than 500 law enforcement, treatment, and health-related agencies cooperated in the reporting effort, yielding almost 900,000 reports on approximately 300,000 individuals. More than 95% of the reported individuals were using heroin. Interestingly, the demographic characteristics of the individuals reported to the Narcotics Register from 1964 through 1967 resemble very closely the decedents who died of narcotism from 1950 through 1961, as shown in the first two columns of Table 1. The gender ratio and the median age are very similar. However, the number of deaths in the Hispanic group increased from about 8% in the interval from 1950 through 1961. The Narcotic Register recorded a 26% increase during the years 1964 through 1967.

The Recent Past: 1970s–1990s

Over the last three decades, important changes have taken place in the population of heroin users, the quality of street-level heroin and the preferred mode of use. The sections below highlight these changing trends.

A. Demographic Trends

Table 1 also shows recent demographic findings for New York City heroin users, in the last years of the Narcotics Register (1971 through 1974), and in admissions to treatment programs in the 1980s and 1990s (4–7). The treatment data show the appearance of a population somewhat different from that of the earlier years. First, females represent a larger proportion of the heroin-using population in recent years, particularly among those entering treatment. Second, the ethnic composition of this more recent population is different, with Hispanics now as the modal group. Finally, the median age of this population increased from 32 to 37 years, as shown by the treatment admission findings from 1986 to 1998.

B. Trends in Heroin Purity

New York City remains the major port of entry and distribution center for much of the

TABLE 1
Demographic Trends of Heroin Users in New York City From Multiple Sources, 1950–1998

	Decedents 1950-1961 (Ref #2)	Reports to Narcotics Register 1964-1967 (Ref #3)	First Reports to Narcotics Register 1971-1974 (Ref #4)	Treatment Admissions to New York City State-Funded Programs 1986-1987 (Ref #5)	Treatment Admissions to New York City State-Funded, Federal-Funded and Private Programs	
					1991-1993 (Ref #6)	1996-1998 (Ref #7)
Total	1,586	64,890	145,577	23,057	50,805	58,338
Gender						
Male-%	78	79	77	70	69	71
Female-%	22	21	23	30	31	29
Race/ Ethnicity-%						
White	21	24	28	23	28	27
Black	39	50	42	31	29	30
Hispanic	8	26	15	45	40	42
Other/ Unknown	32	NA	15	1	3	1
Median Age years	27	27	22	32	34	37

heroin coming into the United States (8). The quality, however, had been relatively low until the 1990s. Fig. 1 shows the dramatic increase in potency in New York City, especially since the late 1980s — from an average purity of less than 10% before 1988 to more than 60% over the last several years. In the past, only a few areas were serving as sources for heroin coming into this country. From the mid-1960s to the 1970s, Turkey was the primary source country, followed by Mexico in the mid-1970s. Since then, however, Pakistan, Afghanistan, Iran, Thailand, Burma and Laos have been exporting heroin to the U.S. The latest addition to this list is Colombia, South America, with sample street-level purity that is practically the highest in the world.

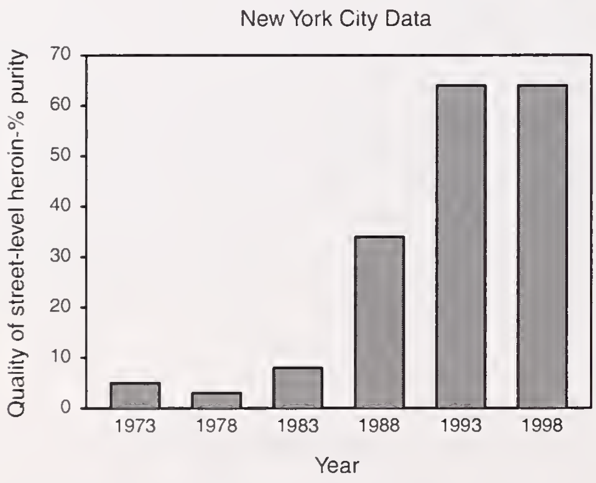

Fig. 1. Purity of heroin obtained on the streets in New York City for the years indicated.

Also, smuggling is now in the hands of new groups that no longer have the monopoly enjoyed by traditional organized crime groups in the past. Each source area, whether from Southeast Asia, Southwest Asia or Colombia, has developed or is in the process of developing competing distribution networks based on ethnic, familial and tribal relationships. The Drug Enforcement Administration has identified Chinese, Albanian, Sicilian, Dominican, Russian and Nigerian groups, among others, that have developed separate distribution networks (8). The result is the ready availability in New York City of high-quality heroin at prices that average well under $1 per milligram of pure heroin.

C. Trends in Modes of Heroin Use

Originally, heroin use was synonymous with injecting drug use. More recently, the intranasal route (heroin sniffing) has become much more frequent. The availability of high purity heroin has encouraged the use of heroin by this route, thereby avoiding the problems associated with transmission of diseases promoted by unsterile intravenous injections.

The trend has moved most decisively to intranasal use, as reported by treatment admissions in New York City, with heroin as the primary drug of abuse. Fig. 2 shows the mode of heroin use reported by primary heroin admissions between 1988 and 1998. Injection declined from 71% to 39%, while inhalation increased from 25% to 59%. Fig. 1 indicates that heroin purity increased dramatically during this period.

Clearly, the quality of currently available heroin has given rise to an alternative to heroin use by injection, but the spread of AIDS among injecting drug users has probably played a major role in discouraging drug injection. As of the first quarter of 1999, the New York City Department of Health has reported a total of 110,395 adult cases of AIDS and 1,924 pediatric cases (9). Injecting drug use is the major risk factor for 47% of the adults (51,504 adults) and 65% of the children (1,249 children), whose parents had been involved in injecting drug use or were the partners of injecting drug users. Unprotected sexual activity between male homosexual partners is the second leading risk factor, representing 32 % of the adults cases. Approximately 63 % of New York City's AIDS patients succumbed between 1980 and 1999.

A direct measure of the decline in overall injecting drug use in New York City is evident from drug treatment admissions data. In 1992, for instance, 25% of all treatment admissions reported injecting as their primary mode of use, regardless of specific drug of abuse; by 1998, 17% reported injecting. Of those who inject, however, heroin remains by far the drug that is most often injected (10).

Interestingly, treatment admissions show ethnic differences by mode of heroin use. Whites, as presented in Fig. 3, are more likely to inject heroin than use it intranasally (38% of injectors were white compared to 19% of sniffers in 1998). In contrast, Hispanics and blacks are more likely to use heroin intranasally than inject it (47% of sniffers were Hispanic compared to 36% of injectors; 32% of sniffers were black compared to 24% of injectors).

D. Cocaine Trends and Heroin Trends

To understand New York City's heroin trends in the recent past, it is also necessary to follow recent cocaine trends. In fact, current trends in heroin activity are probably related to the increase of cocaine activity in New York City in the mid-1980s (11).

Table 2 shows the trends, as indicated by hospital emergency department admissions, arrests and treatment admissions specifically involving cocaine and involving heroin, for the past several years in the New York City area. At the beginning of this period, cocaine emergency department episodes were three times the number of comparable heroin episodes and cocaine-involved arrests were almost twice the number of heroin-involved arrests. By the end of the period in 1998, all trends generally show increases with a final leveling off.

There are several reasons why heroin trends seemed to follow cocaine trends over the past decade or so. First, for cocaine users, heroin had helpful or healing effects. After extended cocaine use and days of sleeplessness, hyperactivity and paranoia, the soothing effects of heroin were very much appreciated by cocaine users (11). This need among cocaine users may have spurred increased heroin use. Second, the up and down or

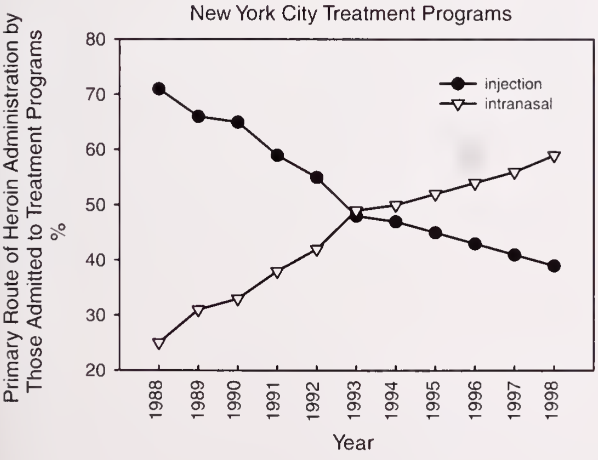

Fig. 2. Route of heroin self-administration for those undergoing treatment in New York City in the years indicated.

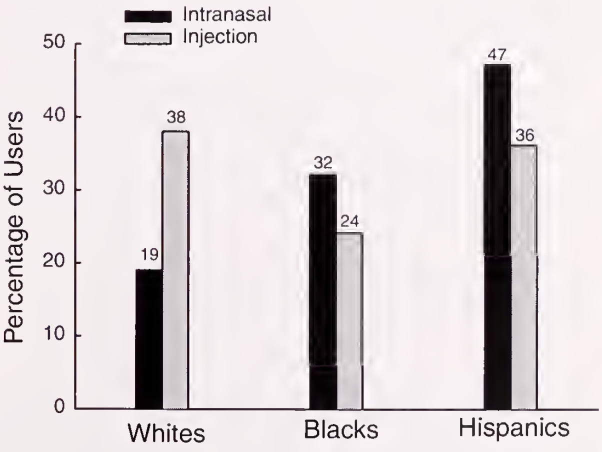

Fig. 3. Data from 1998. Mode of heroin self-administration by ethnic groups.

TABLE 2
New York City Data for Cocaine and Heroin

	Emergency Department Mentions		Arrests		Treatment Admissions	
Year	Cocaine	Heroin	Cocaine	Heroin	Cocaine	Heroin
1988	16,917	5,394	49,014	25,152	NA	NA
1989	14,925	5,437	53,915	28,083	NA	NA
1990	12,633	3,810	46,348	24,421	NA	NA
1991	16,099	6,019	37,769	23,622	15,742	16,142
1992	20,413	8,382	33,708	23,509	17,910	16,974
1993	21,085	11,351	31,296	24,595	16,706	17,689
1994	20,214	11,185	38,200	33,206	17,853	18,956
1995	19,723	10,728	40,846	38,131	17,636	18,495
1996	21,592	11,167	38,813	37,901	17,383	18,707
1997	20,202	9,491	35,431	35,325	16,785	20,052
1998	19,549	9,244	35,377	37,483	16,596	19,726

NA—not available

"speedball" effects of heroin and cocaine together — especially for the injectors — has long been a preferred combination among drug users (11). Third, drug dealers in New York could more easily accommodate the demand for both drugs when Colombia, with its long-standing coca cultivating, started producing opium poppies (12).

Although cocaine has long been a secondary drug of abuse for many heroin addicts, more recently this pattern has been showing signs of moderating. Primary heroin admissions to New York City treatment programs, for instance, show these declines. In 1992, 52% of primary heroin admissions to treatment reported cocaine as the secondary drug of abuse; by 1995, the comparable proportion was 44%, and in 1998 it was 39%. This change may be due to the decline in injecting heroin, as discussed above, and the increase in intranasal use of heroin. Although heroin users have tried to use a combination of heroin and crack/cocaine to achieve a "speedball" effect, this practice has not become widespread. Also, the more recent perception of crack/cocaine as a lowly drug in the hierarchy of drugs may be a deterrent for status-conscious heroin users (13).

E. Trend in Prevalence of Heroin Abuse in New York City

In the mid-1970s, the prevalence of heroin abuse in New York City was estimated to be about 200,000. This estimate was based on reports to the New York City Narcotics Register, using a capture-recapture method to account for "hidden" heroin abusers who had never been reported to the Register (14).

More recently, efforts have been made to update the estimate of heroin abuse. Research was undertaken by the New York State Office of Alcoholism and Substance Abuse Services in 1997 to develop an estimate of heroin prevalence based: (a) on the State's treatment population with primary heroin abuse; and (b) on a qualitative study in which 1,035 interviews were carried out among heroin abusers in 12 communities in New York State. The characteristics of heroin abusers were based on respondents' reports of heroin abusers they knew. Based on these interviews, it was estimated that 24% of heroin abusers were currently in treatment. Based on treatment data, there are approximately 49,000 heroin abusers currently in treatment in New York State. Therefore, given this information, the total number of heroin abusers for the State is estimated to be about 200,000 (15). For New York City, with about 80% of the State's heroin abusers, the current estimate is about 160,000. With the deaths of more than 30,000 injecting drug users in New York City due to AIDS and the general aging of heroin abusers entering treatment, a current estimate of the number of heroin abusers in the City is now predicted to be less than the original 200,000 thought to be the case in the mid-1970s.

The Future

Substantial changes have taken place in New York City's heroin scene, especially over the past three decades. As already discussed, the purity of retail-level heroin has exceeded 60% for most of the 1990s. The impact of AIDS among injecting drug users coupled with heroin's high purity have been major factors in causing the dominant mode of use to change from injecting to intranasal use. Finally, heroin abusers are an aging population, with a median age well into the thirties.

Given these changes, what can be expected in the future? If heroin purity remains high, the likelihood is that "snorting" heroin will continue to be the dominant mode of use. Also, continued experimentation with modes of use other than injecting, such as "smoking," will probably take place as will combinational use with cocaine and other drugs to simulate the "speedball" effect. New York City's heroin abusers, however, will probably continue to be an aging population for the next decade or so. A major factor is the avoidance of heroin among inner-city youth and young adults.

Golub and Johnson have studied the trend using arrestee data for Manhattan's criminal justice system (16). They identify three inner-city cohorts: the first, born in the years from 1945 through 1954 who are the "Heroin Injector Generation"; the second, born in the years from 1955 through 1969 who are the "Cocaine/Crack Generation"; and the third, born since 1970 who are essentially the marijuana or "Blunt Generation." The latter cohort is unlikely to fill the ranks of the earlier cohorts. Boyle and Brunswick offer the explanation that inner-city youth have witnessed the consequences of addiction among parents and older siblings, and have successfully resisted these patterns of drug abuse (17).

In the years to come, a different heroin abuser may become more prominent. It is likely that the New York City suburbs and the less urban areas throughout the state and nation will see more heroin abusers. A recent series of focus groups among professionals in the drug abuse field held by the New York State Office of Alcoholism and Substance Abuse Services throughout the upstate and downstate regions repeatedly discussed the increase in heroin use especially among young adults from affluent suburbs (18). Interestingly, treatment admissions with heroin as the primary drug of abuse are increasing at a faster rate in the several counties closest to New York City than comparable treatment admissions in the City. In the five counties closest to New York City, the number of primary heroin admissions to treatment increased 86% (from 4,480 to 8,333) between 1994 and 1998; during the same period the comparable admissions to New York City treatment programs increased 16% (from 16,974 to 19,726) (10).

Possible explanations for heroin's new attraction include the fact that the inhalation or "snorting" of heroin has made the drug more appealing, and has placed it in the category of powder cocaine. Also, the fashion industry has promoted a "chic" image for heroin. Although there has been an effort on the part of the industry to withdraw the image, the image remains, especially for the young who are fascinated with New York City style and trends (19). Also, there is some evidence that heroin has become used more commonly among the young, especially abroad. Davey and Davies cite reports (20) that in Australia, for instance, "heroin is being used as a 'party drug' by young people who are breaking with the traditional usage stereotypes." Hartnoll cites reports (21) in Europe, "from several countries for increased heroin use, especially smoking, among new young groups."

Thus, a new and young subgroup may be gaining prominence among heroin abusers. Perhaps the dangers of the drug are not appreciated by younger generations and educational efforts are not effectively underscoring the drug's addictive potential and tragic consequences. It is clear that strong and continuing prevention efforts targeting heroin use are needed.

In the event that heroin purity declines and returns to 1970 and early 1980 levels, the likelihood of heroin abusers turning to injection as the mode of use is much greater. With an increase in this mode of use, the host of health, social and criminal consequences that New York City knows all too well from the past will surely exacerbate. In any case, regardless of heroin purity, New York City is likely to remain the major center of heroin activity in the United States.

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Methadone Maintenance Treatment (MMT):

A Review of Historical and Clinical Issues

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Abstract

Methadone maintenance has been evaluated since its development in 1964 as a medical response to the post-World War II heroin epidemic in New York City. The findings of major early studies have been consistent. Methadone maintenance reduces and/or eliminates the use of heroin, reduces the death rates and criminality associated with heroin use, and allows patients to improve their health and social productivity. In addition, enrollment in methadone maintenance has the potential to reduce the transmission of infectious diseases associated with heroin injection, such as hepatitis and HIV. The principal effects of methadone maintenance are to relieve narcotic craving, suppress the abstinence syndrome, and block the euphoric effects associated with heroin. A majority of patients require 80–120 mg/d of methadone, or more, to achieve these effects and require treatment for an indefinite period of time, since methadone maintenance is a corrective but not a curative treatment for heroin addiction. Lower doses may not be as effective or provide the blockade effect. Methadone maintenance has been found to be medically safe and nonsedating. It is also indicated for pregnant women addicted to heroin.

Reviews issued by the Institute of Medicine and the National Institutes of Health have defined narcotic addiction as a chronic medical disorder and have claimed that methadone maintenance coupled with social services is the most effective treatment for this condition. These agencies recommend reducing governmental regulation to facilitate patients' access to treatment. In addition, they recommend that the number of programs be expanded, and that new models of treatment be implemented, if the nationwide problem of addiction is to be brought under control. The National Institutes of Health also recommend that methadone maintenance be available to persons under legal supervision, such as probationers, parolees and the incarcerated.

However, stigma and bias directed at the programs and the patients have hindered expansion and the effective delivery of services. Professional community leadership is necessary to educate the general public if these impediments are to be overcome.

Key Words: Methadone maintenance, heroin addiction, history, pregnancy, evaluation, HIV, hepatitis C.

Introduction

THE PURPOSE OF THIS PAPER is to review historical and clinical issues, basic studies, evaluations, and procedures that led to the development and expansion of methadone maintenance treatment for heroin addiction. This review concentrates on the early development of the program and factors leading to its success and acceptance. From its inception, methadone maintenance treatment has been studied for medical safety and efficacy. The studies investigated not only medical and clinical issues but also the social factors (such as employment and criminality) that affect patient adjustment to the program.

Historical Background of Methadone Maintenance Treatment

Intravenous abuse of heroin intensified in New York City after World War II and, by the 1950s and 1960s, reached epidemic proportions (1, 2). From 1964 to 1970, the names of more than 151,000 addicted persons were reported to the Narcotics Register of the New York City Department of Health (2). Between 1950 and 1961, the death rate associated with the injection of heroin increased from 7.2 per 10,000 deaths to 35.8 per 10,000 deaths, with 75% of the deaths in the 15–35-year-old age group. During this interval, death related to heroin injection became the leading cause of death in New York City for young adults. The average age of death from heroin-related use was 29 years for both sexes (3).

Methadone, a long-acting agonist with a half-life of about 24 to 36 hours, was synthesized for analgesia prior to World War II in Germany. In 1949, Isbell and Vogel, working at the U.S. Public Health Hospital in Lexington, Kentucky, showed methadone to be the most effective medication for withdrawing addicts from heroin (4). The proce-

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dure was to prescribe decreasing doses of methadone to heroin addicts over a week to 10 days or more. This protocol was followed in many institutions. However, follow-up studies in the 1950s and 1960s, from the programs operated at the U.S. Public Health Hospital in Lexington, Kentucky and the Riverside Hospital in New York City, showed relapse rates of more than 90% after patients left treatment (5–10). Civil commitment programs for heroin addicts established in California and New York during the same period showed similar results (5, 9). There were no published scientific reports at the time about the cure rate of the Synanon-type therapeutic communities established to treat hard-core heroin addicts. And New York City jails were filled with untreated heroin addicts (9).

In 1958, the Joint Committee of the American Bar Association and the American Medical Association issued a report recommending that an outpatient facility be established to prescribe narcotics on an experimental basis. In 1955 and 1963, the New York Academy of Medicine recommended that clinics be established in affiliation with hospitals, to dispense narcotics. In 1956 the American Medical Association, and in 1963 President Kennedy's Advisory Commission, made similar recommendations (5, 11).

Methadone maintenance began as a research project at The Rockefeller University in 1964, under the joint direction of Dr. Vincent P. Dole and Dr. Marie E. Nyswander. The initial research project was funded through the Health Research Council (HRC) of New York City in response to the burgeoning post-World War II heroin addiction epidemic. Dr. Lewis Thomas of the HRC appointed Dr. Dole chair of the Narcotics Committee of the council. He was asked to investigate the heroin epidemic in New York City and to determine whether an effective medical intervention could be developed (11). In 1988, Dr. Dole received the Lasker Clinical Research Award for postulating the physiological basis of narcotic addiction and pioneering the development of methadone maintenance treatment for heroin addiction.

Dr. Mary Jeanne Kreek, a first-year medical resident at New York Hospital-Cornell Medical Center in internal medicine and neuroendocrinology, was enlisted in 1964 to participate in the research (11, 12). Dr. Kreek is now Professor and Head of the Laboratory of the Biology of Addictive Diseases at The Rockefeller University.

Six male heroin addicts, with an average of more than eight years of addiction and histories of arrests, voluntarily enrolled in the pilot study in 1964 at The Rockefeller University. The research team first reexamined earlier clinical trials carried out at the U.S. Public Health Hospital at Lexington, Kentucky, where the feasibility of controlling heroin addiction with short-acting narcotics had been addressed. They then prescribed morphine, which is chemically related to heroin, to the first two patients as a maintenance medication. This proved unsatisfactory, since morphine had to be injected several times per day in increasing amounts as tolerance developed. Furthermore, the patients were apathetic, sedated, and preoccupied with receiving the next injection to avoid experiencing withdrawal symptoms. With the failure of short-acting narcotics as a maintenance medication, long-acting narcotics such as methadone were investigated (11, 12). Methadone, as previously indicated, was being used as a safe, effective medication to withdraw addicts from heroin. But instead of discontinuing the methadone, as was then the custom, the research team maintained the patients on methadone so that its effects could be studied. As the patients developed tolerance to methadone's narcotic properties, they were no longer sedated or preoccupied with drugs. Their affect was clear, their behavior changed and they began to plan for employment and school. Most important, their drug craving was relieved. Four additional patients were then treated with and stabilized on methadone at The Rockefeller University. The same results were obtained. Eventually, the six patients found jobs while they were maintained on methadone doses of 100–180 mg/d.

To test whether methadone would prevent relapse to heroin addiction or respiratory depression if heroin was tried again, rigorous double blind studies were conducted. The effects of the following opiates, while patients were on methadone, were tested in a Latin square design protocol: heroin, morphine, dilaudid, methadone, and saline. An effective blockade effect was noted at 80–120 mg/d, or over, against the narcotic effects of heroin, morphine, dilaudid and methadone itself. Significantly, the patients did not experience respiratory depression (13).

Prior to and during the course of these studies, Dole, who had previously studied the metabolic factors involved in obesity, speculated that the craving reported by addicts and the effects of the protracted abstinence syndrome described by Martin (14) were symptomatic of a metabolic alteration within the central nervous system (9, 15). Dole also predicted the existence, location and density of opiate receptors in the brain.

The principal effects of daily methadone dosing in maintenance treatment were determined from the team's initial research (11–13, 16–18). For most patients, the amount of methadone prescribed orally, usually between 80–120 mg/d, should be sufficient to:

- relieve narcotic craving
- suppress the opioid abstinence syndrome for 24–36 hours
- block the effects of administered heroin
- develop tolerance to the euphoria, sedation or other narcotic effects of methadone which would impair emotional responses, functioning or perception
- develop tolerance to the analgesic properties of methadone

However, some patients might need higher doses to achieve these effects. Others would be able to function normally on lower doses of 60 to 80 mg/d. In 1990, the Government Accounting Office (GAO) in a review of methadone programs nationwide reported that the lowest effective dose for maintenance treatment was 60 mg/d.(19). Once an adequate dose of methadone has been achieved, there should be no narcotic effects noticeable to either the patient or observers of the patient in interactions of everyday life. Properly stabilized methadone patients who are not abusing drugs and alcohol experience normal emotions and acute and chronic pain. It should be noted that a blocking dose of methadone is dependent on the strength and amount of heroin that is used. Thus, during certain periods when street heroin is especially pure and/or inexpensive, higher doses may be needed to achieve blockade.

In 1965, Dr. Ray Trussell, then the New York City Commissioner of Hospitals, transferred the research pilot project from The Rockefeller University to the Morris J. Bernstein Institute of the Beth Israel Medical Center, for expansion and further evaluation. At the Bernstein Institute, an outpatient clinic model was opened; it was staffed by a physician, nurses and counselors to assist patients with their addiction and their medical, personal and social problems. In 1965, all patients in the Beth Israel program were treated with methadone for six weeks as inpatients before being discharged to the outpatient clinic. In 1966, initiation of treatment with methadone was transferred to the outpatient clinic. Evaluation of both methods showed no significant differences in outcomes (21). In 1966, the clinic model was adopted for expanding methadone maintenance treatment throughout the United States.

By 1998, the number of methadone patients in the United States had increased from the original six research patients (16) in 1964 to about 44,000 patients in New York State and179,000 patients nationwide (22). The IOM report (18) estimated that there are between 500 thousand and one million or more heroin users in this country. If this is the case, only 18 – 36 % of these heroin users are enrolled in methadone treatment. Methadone maintenance is now recognized as the most effective treatment for heroin addiction, as validated in reviews by the Institute of Medicine (IOM) (18) and the National Institutes of Health (23).

Criteria for Admission

Admission criteria are now much more liberal than they were under the original research protocols, which limited applicants for admission to those between the ages of 21 and 40 with a minimum of four years of narcotic addiction. Excluded were those who had problems of alcoholism, mental illness or polydrug abuse. Patients originally had to have had episodes of prior treatment (e.g., detoxification from heroin or treatment in residential therapeutic communities) to qualify for admission. These original criteria were constructed to include hard-core addicts who were unable to abstain from using heroin, and to test the efficacy of methadone in a relatively "pure heroin addict." The upper age limit was based on a theory that addicts "mature out" of addiction over the age of 40. During the ensuing years, as groups of patients were successfully treated, admission criteria were relaxed to include younger and older addicts. Heroin addicts with mental health and polydrug abuse problems, including alcoholism, also became eligible for acceptance. The current criteria have been established by the federal and state governments. State regulations (24) may not be more liberal than the federal mandates. In New York State, the regulations are as follows:

- Applicants age 18 and over must document at least one year of opioid addiction, mainly to heroin. This can be documented: by history provided by the patient and/or the statements of family members or friends; records of prior substance abuse treatment including detoxification and entry into different types of programs; signs of withdrawal or over-sedation; results of a urinalysis test taken at the time the applicant applies for entry; and needle marks or tracks on various parts of the body and/or erosion or severe irritation of the nasal septum, indicating that the patient has inhaled heroin over a long period of time.

- Applicants between the ages of 16 and 18 require a two-year documented history of addiction, parental consent, and two previous unsuccessful treatment experiences.
- Pregnant, heroin-using applicants need to document current addiction and can be admitted to treatment with less than one year of heroin use if evaluated and approved for admission by the physician of the clinic. Upon giving birth, they will be reevaluated for continued treatment.
- Serious psychiatric co-morbidity and/or a history of abuse and addiction to substances other than opioid (e.g., cocaine and alcohol) may not exclude applicants from entering treatment. Once admitted, patients in this category would be treated for these conditions in the clinic, if appropriate, or referred to other agencies for psychiatric therapy and/or detoxification from other drugs. Methadone maintenance treatment (MMT) would be continued in the clinic while they were being treated for their co-morbid conditions.
- Applicants terminated from prior treatment for noncompliance with program regulations must be reevaluated before readmission and, if found not acceptable, may be referred elsewhere for treatment.

Proof of current addiction is not required of individuals who have prior histories of heroin addiction and treatment, and feel they are in danger of relapsing to heroin. This category includes applicants who were discharged from institutions, and former patients who successfully left methadone treatment within a two-year period and feel they are in danger of drug relapse.

Intake Procedure

Once the applicant meets the criteria for admission, he or she is provided with an orientation to MMT, as well as a handout of the regulations and services of the program, and is asked to sign various consent forms agreeing to program policies and allowing for the administration of methadone. The patient also receives a physical examination, which includes complete blood chemistries and testing for hepatitis, venereal diseases, tuberculosis, and pregnancy. A tetanus shot is provided to all patients. Urine tests are taken to verify the presence of opioids and other drugs. HIV testing is offered subsequent to admission, with the patient's consent, following an orientation about the test and the disease of AIDS. The patient begins treatment upon completion of the admission procedure. A psychosocial assessment and treatment plan are completed within 30 days of admission.

Once accepted, patients report daily to the clinics and drink their prescribed doses of methadone, observed by a nurse. Reporting schedules are liberalized for patients who are compliant and show improvements in functioning. Eventually, patients can report once per week and receive six liquid doses in vials to take home for daily consumption. Patients submit a minimum of eight urine specimens a year, which are tested for the presence of methadone and illicit drugs, including heroin.

The Methadone Induction Process

At the beginning of treatment, patients present different levels of heroin dependency to the clinic staff. Therefore, the physician and staff must evaluate patients in order to determine the proper initial dose of methadone that will begin to relieve the abstinence syndrome of heroin and narcotic craving without inducing sedation. The patient may be prescribed a starting dose of up to 30 mg, which can be supplemented by an additional 5 – 10 mg after a two-hour observation period if abstinence symptoms persist. Also, the observation period is required by federal regulations to ensure that the patient is not sedated. By government regulation, the first dose of methadone cannot exceed 40 mg.

Based on observation of the patient for the presence of sedation or the persistence of the abstinence syndrome, doses can be increased by 5 – 10 mg every day or every other day, up to a dose of 60 mg. After this level is reached, dosing takes place on an individual basis until the patient reaches a level — usually 80 – 120 mg/d or above — where the three principal effects of methadone are achieved: relief of craving, blocking of narcotic effects of heroin, and relief of abstinence syndrome. If the dose increase is too rapid, the patient may experience transient episodes of urinary retention, edema and abdominal distention. Therefore, the build-up process to an adequate maintenance dose must be carefully calibrated to the needs of the individual patient (16, 25).

Major Evaluations

In 1965, an impartial committee was organized, headed by Dr. Henry Brill of the New York State Department of Mental Hygiene, to evaluate the methadone maintenance program. The evaluation itself, which began in August of 1965, was conducted over a period of six years by Dr. Frances Rowe Gearing of the Columbia University School of Public Health. Dr. Gearing reported semiannually to Dr. Brill's committee (21).

A final report was issued in 1974 (21), by which time some 17,500 patients had been admitted to methadone treatment in the five counties of New York City, plus Nassau, Suffolk and Westchester counties, during the period from January 1964 to December 1971. The following are highlights of the report:

- As of December 1973, there was an overall 77% retention rate of patients in treatment.

- For the first 1,230 patients admitted to the program, there was a 35% improvement in productive behavior — employment, education and homemaker status for women — compared to the patient's status at the beginning of treatment. Increases in social productivity at the end 1973 were recorded for all cohorts of patients admitted annually from 1964 through 1971.

- Arrest rates dropped from 201 arrests per 100 person-years prior to entering treatment to 1.24 arrests per 100 person-years after entering methadone treatment. About 75% of the patients were not arrested. In the three years prior to entering treatment, all patents had records of criminal arrests.

- The follow-up status of the first 356 patients who left treatment showed that few if any were free of problems related to addiction and criminality: 38% were arrested, 26% had records of detoxification after relapse to heroin, 15% were in other types of drug treatment programs that did not offer methadone, 6% had died, 7% returned to methadone treatment.

- About 25% of the patients presented with alcoholism and non-opioid drug abuse (e.g., barbiturates, amphetamines, and cocaine problems). These problems were the major causes of discharge from the program. Alcoholism was a major problem for patients over age 30 and also among black patients, while non-opioid drug abuse was a major problem among white patients under age 30.

- In the early 1970s, an increasing proportion of patients entered methadone treatment with serious life-threatening illnesses, including heart disease, cancer, and neurological and other conditions. This trend highlighted the need for methadone programs to be affiliated with hospital and medical backup facilities.

- The death rate of patients in treatment was slightly higher than the death rate of the New York City population aged 20–54 between 1969 and 1970 (7.6 vs. 5.6 deaths per 1,000 population). However, the death rate of patients who left treatment was more than three times the rate of patients in treatment (28.2 deaths per 1,000 population). And 64% of the ex-patient deaths after leaving treatment were probably drug related as opposed to 30% of the deaths of patients in treatment.

In 1978, Dole and Joseph reported their study of 846 randomly selected patients who were discharged for a variety of reasons from methadone clinics in New York City (26). The following was noted at the time of the interviews and examination of community agency records at an average of approximately two years after the patients had left MMT.

- Only 8% of the discharged patients appeared to be doing well, had not relapsed to the use of heroin, were free of alcohol or non-opiate drug problems, and had not been rearrested.

- 64% had relapsed to the use of heroin and were re-addicted; 6% were using heroin once or twice per week; 22% had other serious problems related to alcohol, non-opioid drugs and crime.

- About 66% of the patients who had left "in good standing" were either re-addicted to heroin, were using heroin once or twice per week or were involved with serious alcohol, non-opiate drug problems and crime, while 98% of the patients who had left for cause were involved with these problems after leaving treatment. Conversely, 34% of the patients who had left in good standing and 2% who had left for cause were apparently well, with no problems related to addiction or criminality.

- Duration of heroin addiction, length of time in methadone treatment and type of termination from methadone treatment (e.g., in good standing vs. for cause) appeared to be major predictors of a patient's post-treatment adjustment and relapse to heroin. Gender, ethnicity and level of education were not predictors of post-treatment use of heroin. Patients who had been addicted for less than five years, had remained in treatment three or more years, and had left the methadone treatment program in good standing appeared to have a better chance of doing well (e.g., no relapse to heroin) after leaving treatment compared to patients with longer histories of using heroin, treatment duration of less than three years, and exit from treatment for cause, without proper social supports (e.g., no employment, continued substance abuse and criminal activity).

- Death rates of patients after leaving treatment were more than twice the death rates of patients who remained in treatment. Alcohol-related illnesses were the major causes of death for patients in treatment. Narcotism or heroin overdose was the major cause of death, followed by alcohol-related illnesses, for patients who left treatment, with the highest rate of death occurring during the first month after leaving treatment.

- Alcoholism was a major factor in 26% of the terminations from MMT. It should be noted that more than 80% of the patients who had alcohol problems prior to admission to methadone treatment continued drinking excessively while in methadone treatment.

- Pretreatment arrest rates were higher for patients who had left during the first year of MMT, as compared to patients who remained in treatment for more than one year (1.5 vs. 0.8 arrests per person-year).

- The major predictors of post-treatment heroin use were type of discharge from treatment (favorable vs. for cause), duration of heroin addiction prior to treatment, and employment status at discharge.

In the mid-1980s, an evaluation of the effectiveness of MMT was undertaken by Ball and Ross (27), who investigated the adjustments of 617 male patients in six programs located in three major metropolitan areas with large populations of heroin addicts — New York City, Philadelphia and Baltimore. Factors examined in this study of methadone treatment included criminality, use of heroin and other drugs, and a follow-up of patients who left treatment during the course of the project. The administration of the six programs and the services that were offered were also investigated.

- 77% of the patients stopped their intravenous use of heroin over a period of six months. After 4.5 years of treatment, 92% had stopped heroin use, 96% reported no use of barbiturates and amphetamines, and 83% were not using cocaine. Dosage of methadone was an important factor in reducing heroin use, irrespective of the program in which patients were enrolled. For a 30-day period prior to patient interviews and medical record checks within the first months of the study, 28% of the patients receiving doses of methadone of less than 45 mg/d were using heroin as opposed to 5.4% who were on doses of at least 46 mg/d. However, there was no heroin use in the subgroup of patients receiving 71 mg/d or more of methadone.

- For patients enrolled in methadone treatment for six months or more in this study, there was a 79% reduction in all types of crime from pre-treatment levels. Reduction of crime was related to time in treatment, with patients in treatment three or more years committing fewer crimes than patients in treatment less than three years.

- 82% of 105 patients who had left methadone treatment relapsed to heroin addiction within 12 months. Of the 23 patients in this group who had left in good standing (e.g., socially rehabilitated, not abusing drugs, responded to counseling and completed withdrawal from methadone), 16 (69.5%) relapsed within the course of the year following treatment. Seven (30.4%) had not relapsed.

Ball and Ross noted that the administration and policies of programs influenced patient outcomes. Those programs with developed services and committed staff achieved better results. Favorable outcomes were better correlated with the extent and quality of the services offered by the programs than with patient characteristics at admission. These researchers expressed the view that additional quality services were needed in the programs.

Length of Treatment and Methadone Dose: Implications for Treatment

The studies by Gearing and Schweitzer (21), Dole and Joseph (26), and Ball and Ross (27) demonstrate that methadone maintenance is a corrective therapy, not a curative therapy. That is, the vast majority of those who withdraw from methadone will relapse to heroin use (28). While shorter use of heroin and longer treatment with methadone and social stability are correlated with abstinence in a small number of patients, there are no clear predictors of success (26). However, D'Aunno's 1995 study of selected clinics in the U.S. found that a majority of clinics encourage withdrawing after only one year of treatment (29). Patients may also be withdrawn for noncompliance with treatment — including continued use of illicit drugs or even failure to become employed (30).

Methadone dose has been shown to be an important factor in retaining patients in treatment. Watters and Price reviewed 44 methadone programs in the United States and found that dose level was the single most important factor affecting retention in treatment. The higher the dose of methadone, the longer patients remained in treatment (31). Caplehorn and Bell reported the same phenomenon in Australia (32). Patients stabilized at 80 mg/d or more had higher retention rates in treatment than patients who were on lower doses and had used less heroin. Factors associated with good patient outcomes, such as employment, level of education and reduction in criminality, appeared to have less of an effect on retention than did the level of dose. Leavitt et al. report that doses in excess of 100 mg/d, even as high as 780 mg/d, are safe and necessary to eliminate opiate abuse and, in some cases, reduce abuse of alcohol and other drugs (20). Hartel et al. have shown that methadone doses of more than 80 mg/d help protect patients from acquiring HIV, as compared to lower doses (33).

Despite this evidence, many programs do not adhere to medically sound dosing protocols. D'Aunno also found the average daily dose in the majority of clinics surveyed to be 59 mg, which is less than the lower end of the therapeutic range of doses. Additionally, 66% of the clinics had an upper dose limit of 80 or 100 mg (29), despite the fact that many patients need doses of 100–120 mg, and a smaller number need much higher doses. Furthermore, research protocols are still being carried out which randomize patients to ineffectual doses as low as 20 mg, 30 mg and 50 mg. (34, 35). In contrast, the Office of Alcoholism and Substance Abuse Services (OASAS) of New York State has obtained a waiver allowing physicians in methadone programs to prescribe up to 150 mg/d of methadone for those patients who continue to use heroin. Doses above that level require state notification, with justification.

Polydrug Abuse

Among heroin addicts, the frequent use of non-narcotic substances has been documented as far back as 1967 by Langrod et al. (36). They reported that 91% of 413 heroin addicts committed to the New York State Civil Commitment Program admitted to having used other drugs, with 55% using four or more illicit drugs. Among patients receiving MMT, examination of the latest available data indicates that about 40% of methadone patients use cocaine or crack upon admission to the program. Kreek et al. indicated that in the 1970s about 20% of the methadone patients had serious alcohol problems upon admission to the program (37). Joseph and Appel found that alcohol-related diseases were major causes of death of patients in methadone treatment, and that approximately 23% of the terminations from treatment were related to alcohol (38). Since polydrug and alcohol abuse exist prior to admission to the methadone program, the extent of the problem needs to be assessed and appropriate treatment methods applied when patients enter treatment. Also, patients with serious problems of anxiety or depression may turn to the abuse of illegal substances if they are not properly diagnosed and treated. Treatment should include psychiatric care and medication as well as detoxification from non-prescription substances and behavioral interventions as needed. In New York State, methadone patients who are alcoholics can now be admitted to inpatient programs of Addiction Treatment Centers. However, there are no effective long-term medical interventions for cocaine addiction. Nevertheless, sharp and significant reductions in cocaine use have been reported in a cohort of 133 methadone patients who remained in treatment for 18 months and received adequate doses of methadone (39). Cocaine-using methadone patients may also reduce their use of cocaine by participating in individual counseling, a Cocaine Anonymous group or cognitive therapies (40).

Impact of MMT on the Community

While it is important for the practitioner to be aware of how the patients fare on the program, the impact on public health and safety within a community can only be inferred. In New York City, from 1971 through 1973, there was a 142% increase of patients, from 14,000 patients up to about 34,000, as a result of a rapid expansion of methadone clinics under the direction of Dr. Robert Newman of the former Health Services Administration. In the 1970s, estimates of the number of heroin addicts in New York City varied from about 164,000 to 203,000. Therefore, in 1973, only an estimated 15 – 18% of the heroin users in New York City were enrolled in MMT. However, the following decreases in social and medical problems associated with heroin addiction, for every 1,000 admissions to methadone programs in the City, were noted from 1971 through 1973:

- Addiction-related property crime (reduced by 3,869 per 1,000 admissions)
- Drug arrests (reduced by 1,251 per 1,000 admissions)
- Hepatitis (reduced by 75 cases per 1,000 admissions)
- Deaths related to drug dependence (reduced by 16 deaths per 1,000 admissions) (40)

A similar phenomenon was noted in Hong Kong, where reductions in addiction-related property crimes and incarcerations were found after methadone treatment was introduced in 1976 (41).

Diversion

Diversion of methadone has always been a source of concern in the community. The fear of diversion has been a factor in the opposition to the expansion of MMT and the opening of new clinics. However, the Institute of Medicine's (IOM's) report (18) regarding the regulation of methadone treatment suggests that diversion of methadone, while of concern, does not appear to be serious enough to take precedence over accessibility to treatment for untreated addicts. This conclusion is based on data collected from many sources throughout the United States, such as health departments, medical examiners, etc. The IOM report (18) and reports from the street studies unit of the New York State Office of Alcoholism and Substance Abuse Services note the following reasons related to sales or purchases of methadone:

- Patients sell methadone to supplement their incomes.
- Patients may buy methadone to supplement their program doses if they are inadequate.
- Individuals may buy or sell methadone to assist relatives or friends who are in withdrawal and require it.
- Addicted persons who cannot enter treatment because of waiting lists, who do not have Medicaid, and who are unable to afford to pay for their treatment, buy street methadone to stave off withdrawal symptoms from heroin.
- Addicted people buy diverted methadone to maintain themselves outside of a program if heroin is not available. Some addicts buy street methadone to obtain a "high" in combination with other drugs. Other addicted persons may buy methadone because they find program regulations and rules too onerous, or to preserve confidentiality about their addictions by not being identified when entering a neighborhood methadone program.

Thus, diverted methadone is purchased primarily to withdraw and maintain an untreated heroin-addicted population. Primary addiction to methadone is rare, since methadone does not produce the sharp euphoria of heroin. Therefore, regulations based solely on fears of diversion can be counterproductive (18). Availability of MMT should be increased and made more affordable, and doses in treatment should be adequate for the patients' needs.

Two options exist for patients who are not compliant with their methadone treatment regimens. One option is to require that they attend the clinic six or seven days per week with little or no privileges to take out methadone doses. The second option is the use of levomethadyl acetate (LAAM), which can be administered orally in the clinic two or three times per week (42).

Pregnancy

Methadone is the only approved medication for treating narcotic addiction during pregnancy. The use of narcotic antagonists such as naltrexone is contraindicated, since these medications precipitate the opioid abstinence syndrome and can result in spontaneous abortion, fetal distress, premature labor, and stillbirth. The use of LAAM in pregnancy has not been studied. Therefore, women who become pregnant are not eligible to receive LAAM or are transferred to methadone if they become pregnant while receiving LAAM.

The use of heroin during pregnancy subjects the fetus to daily fluctuations of the abstinence syndrome, which can result in stillbirth, premature delivery, low birth weight, and sudden infant death syndrome. The lifestyle associated with heroin addiction during pregnancy can lead to poor nutrition, transmission of infectious diseases, including HIV and hepatitis, and complications such as endocarditis and abscesses from use of contaminated needles. In addition to the fluctuation of opiate levels, destructive lifestyles and the use of other drugs, tobacco and alcohol may result in spontaneous abortion, premature rupture of membranes, intrauterine growth retardation, pre-term labor, breech presentation, and toxemia (43–47).

Methadone in pregnancy has been studied since the late 1960s. The following outcomes have been noted from various studies (43–47):

- Methadone maintenance during pregnancy has the potential to eliminate the use of heroin by injection, smoking or inhalation, as well as help reduce the use of other legal and illegal drugs.

- MMT by itself is insufficient to deal with all the issues that confront a pregnant heroin addict. The patient must be referred to a comprehensive program that includes prenatal and medical care, nutritional counseling, and attention to resolving the many medical, personal and social problems that the patient presents.

- Methadone, because it is a long-acting medication, provides the fetus with an environment for development that is not subject to the fluctuations associated with the abstinence syndrome.

- However, during the course of the pregnancy, there are marked differences in methadone blood plasma levels that have to be closely monitored. A variety of maternal, placental and fetal factors, including an increase in fluid space, a large tissue reservoir, and metabolism by the placenta and fetus may lead to the need for higher doses, particularly in the third trimester. This increase may be required to prevent the manifestation of the opiate abstinence syndrome, which would be stressful to the developing fetus. Kaltenbach et al. (45) stress the need for understanding the metabolic changes and the increase in blood volume during pregnancy, since pregnant methadone patients frequently develop withdrawal symptoms that must be treated with increases in methadone dose.

- Methadone maintenance reduces obstetrical complications that are found in pregnant heroin addicts. Higher maternal methadone doses in the first trimester may result in higher neonatal birth weights (43–46).

Neonates born to methadone-maintained women may or may not experience some form of the opioid abstinence syndrome, usually within 24 to 72 hours or longer after birth. Prolonged observation is essential.

A variety of studies (43–45) have shown conflicting data regarding the correlation between methadone dose and manifestation of the abstinence syndrome. These data range from no correlations with any dose level to a correlation at all dose levels. While this syndrome is not usually fatal in adults, neonates are more sensitive and must be treated if symptoms appear. The neonatal abstinence syndrome can be pharmacologically controlled with medication such as paregoric or phenobarbital. Paregoric is preferred to phenobarbital since few seizures, if any, are observed with the use of paregoric as compared to the greater number associated with the use of phenobarbital. The neonatal abstinence syndrome is brought under better therapeutic control in a shorter period of time with paregoric, and there is a more rapid normalization of the sucking reflexes in paregoric-treated infants (44, 45).

A study of infants who experienced seizures related to the abstinence syndrome following birth, showed early abnormal neurological examinations. However, within the first year, abnormalities disappeared and EEG tracings became normal. Furthermore, infants with seizures during the first year of life did not differ otherwise from those who did not have seizures. This favorable outcome suggests that the long-term prognosis for abstinence-related seizures is better than that for seizures related to other pathologies (46).

Breast feeding of infants is encouraged during the first six months of pregnancy. However, breast feeding is contraindicated if the mother is HIV positive, and/or abusing drugs such as alcohol, amphetamines and heroin, all of which can reach significant levels in breast milk. The rates of the concentration of methadone in milk and plasma, in contrast, have been shown to be low (43- 45, 48). Accordingly, monitoring of methadone levels in the breast milk and infant plasma is not necessary. Weaning should not normally represent a problem with respect to withdrawal symptoms (45, 48).

A follow-up study of 25 four-year-olds whose mothers were maintained on methadone during their pregnancies and who had received prenatal care showed normal development as compared to controls. Neurological examinations, Wechsler Pre-School and Primary Scale of Intelligence, language development and motor-free visual perception tests were administered. The results of all neurological examinations were within normal parameters, and there was no relationship between IQ scores and the severity of the abstinence syndrome at time of birth. There were no statistical differences between the infants exposed to methadone in utero and non-exposed controls: average IQ scores were 106.5 for methadone-exposed infants and 106 for controls. To date, no chronic conditions or abnormalities attributable to methadone have been identified in those children exposed to methadone in utero when their mothers also received prenatal care. However, follow-up studies are needed on older groups of children exposed to methadone in utero compared to normal controls (43, 44, 45).

To summarize, the use of methadone fosters both a healthy infant and a healthy mother. However, methadone can cause some complications in the first weeks of life, but these are medically manageable and preferable to the fluctuations in opiate levels found in heroin addiction and the dangers of the associated lifestyle.

Medical Safety and Side Effects

Medical safety issues regarding methadone maintenance have been monitored since 1964 (18). Long-term methadone maintenance is a medically safe, nontoxic treatment with minor, mostly transitory side effects, found mainly during the induction phase of treatment. In general, the overall health status of patients improves after spending time in treatment (18). The chief complaints are increased perspiration and constipation. While methadone is metabolized by the liver, it is not hepatotoxic; patients entering MMT with normal liver function maintain normal liver function (12, 18). However hepatitis B and C (and in some parts of the country hepatitis delta) are common infections with prevalence rates of up to 80% among heroin injectors (47). Therefore, abnormalities of liver function among methadone patients are usually caused by infections acquired prior to entering treatment and/or as a consequence of alcoholism. There are no toxic effects on the kidneys, though again, patients may enter treatment with chronic renal disease, which is a common problem among heroin addicts (18).

Methadone, when properly prescribed at adequate doses in long-term maintenance treatment, normalizes the physiological functions that are deranged by heroin addiction (12, 18). These include:

- stress responses of the central nervous system and down-regulation of the hypothalamic-pituitary-adrenal axis
- reproductive hormones of the hypothalamic-pituitary-gonadal axis resulting in abnormal functioning
- indices of immune functioning linked to neuroendocrine functioning (18)

The impaired functioning of these systems may be related to the drug-seeking behavior of heroin addicts. Addiction to heroin may cause irregularities in menstrual functioning among women and loss of libido and potency among males. Patients may relate concerns about sexual function. However, the IOM report (18) on methadone indicated that more than 80% of the men and women who reported sexual irregularities while addicted to heroin revert to normal functioning within one to three years: women experience normal menstruation; and libido and potency are restored to the males, although some may report delayed ejaculation (12, 18).

Several researchers investigated sexual problems that MMT patients attributed to the medication. Of the 101 patients reported by Langrod, Lowinson, and Joseph (51), 17% reported problems related to delayed ejaculation and potency at the time of the interview. The patients (with a mean age of 35 years) compared their current sexual functioning to the period prior to heroin use, which was during their teenage years . Other studies note, however, that methadone patients report an increase in libido upon entering methadone treatment, as compared to the period when they were using heroin (12, 18).

Functional Potential of Methadone-Maintained Patients, Employment, and Driving

Methadone patients have been employed in a wide variety of jobs that encompass the range of skills found in the job market. Patients in the

Methadone Medical Maintenance Program are owners of businesses, managers, salespersons, professionals, computer technicians, and blue-collar workers in the building trades (52). An analysis of the jobs held in 1972 by 951 patients known to the New York City Health Services Administration Methadone Program shows that patients were employed across the spectrum of the job market: building trades (14%), municipal government (0.7%), federal government (0.6%), clerical work (4.5%), professional (2.6%), skilled work (17.1%), semiskilled work (5.5%), services and management (3.7%), sales (9.0%), social services (2.7%), and unskilled work (39.4%) (53).

Gordon and Appel found that methadone patients were within the normal range on tests of intellectual functioning, reaction-time studies, tests of sustained attention and perceptual-motor skills (54). In reviews of driving records and interviews with patients not impaired by use of alcohol or depressants, it was found that methadone patients do not differ significantly in the number of accidents or traffic violations compared to age-matched, non-drug-users or former heroin addicts who were not enrolled in MMT and were abstinent.

The first 155 patients to receive methadone doses of 79 mg/d to 100 mg/d tested within the normal range of intellectual functioning (54). There was an absence of patients in the lowest range of IQs. Follow-up testing of 30 patients a decade later showed the following results: 25 scored higher than their original tests, one scored the same, and four showed modest declines within the normal range of scores.

Therefore, the major conclusion of studies concerning the functional potential of methadone patients is that they can perform any job for which they are qualified. Alcohol and depressants are more likely to be a source of problems for persons who drive or work around machinery than is methadone when used as a maintenance medication.

Methadone Maintenance and HIV/AIDS

Studies worldwide have confirmed that methadone maintenance plays a crucial role in the prevention of the transmission of HIV infection among injectors of heroin, reducing the risk 4- to 6-fold (55).

- Abdul-Quader et al. showed that methadone treatment could reduce risk behavior related to injection (56). The frequency of heroin injection and visits to shooting galleries (places where groups of addicts inject drugs and possibly share injection equipment) were reduced over time after enrollment in MMT.

- A prospective study by Metzger et al. (57) compared HIV-negative patients on methadone to HIV-negative heroin users who were not in treatment but who were recruited from the patients' social network. In the course of 18 months, 3.5% of those remaining in treatment seroconverted to HIV positive, while 22% of those remaining out of treatment seroconverted.

- Hartel and Schoenbaum examined HIV infection in a group of 622 methadone maintenance patients in the Bronx who were former injectors of heroin and, in some cases, of cocaine (33). The social and medical data in this study cover a 20-year period back to the beginning of the HIV epidemic in 1978. In this group, a methadone dose of 80 mg/d, or more, played a central role in preventing transmission of HIV. Patients receiving more than 80 mg/d had significantly less HIV infection than patients receiving lower doses. The protective value of adequate high-dose methadone was independent of year of last cocaine injection, needle sharing in shooting galleries, number of injecting drug users who were sex partners, low income, counseling, and minority ethnicity (e.g., Latino, African American). The study emphasized the need for methadone maintenance programs in preventing transmission of disease and helping patients with other social and medical problems.

- Blix and Grondbladh (58) showed that patients who entered methadone maintenance in Uppsala, Sweden prior to 1983 had lower rates of HIV infection and AIDS than those admitted after 1983. The researchers concluded that for patients who remained in treatment, methadone maintenance offered protection against acquiring HIV, since injection of heroin was either eliminated or significantly reduced. The researchers also recommended that untreated heroin addicts enter methadone treatment as a precaution against HIV infection (58).

- Weber et al. conducted a three-year prospective study of a group of HIV-infected methadone patients and a group of HIV-infected heroin addicts (59). The progression to AIDS was faster among the heroin users than among the methadone-maintained patients.

- A study of 58 rehabilitated patients in New York City (e.g., employed, socially stable, not using illicit drugs or injecting heroin) showed that they were seronegative for antibody to HIV (60). These patients had used heroin for an average of more than 10 years prior to entering MMT, before the major onset of the HIV/AIDS epidemic. They were in methadone treatment for approximately 17 years and had stopped injecting heroin. However, prior to entering methadone treatment, they had engaged in high-risk behavior such as sharing needles and, as a result, 91% had markers for hepatitis B. Successful participation in methadone maintenance was therefore associated with an absence of HIV antibody.

- Magura et al. report that cocaine use among methadone patients has been related to a higher prevalence of HIV-risk behaviors (e.g., shared needle use and multiple sexual partners) than among methadone patients who do not use cocaine (61). However, among the cocaine-using population in methadone treatment, needle-related sharing and sexual risk behaviors declined significantly over a two-year period after admission to methadone treatment. The authors recommend that cocaine-using patients be retained in treatment and that services such as access to needle exchange and free condoms be increased. From a harm-reduction perspective, methadone maintenance was effective, even for cocaine-using patients, since injection of heroin declined. Discharge from methadone treatment would have the potential effect of increasing HIV-risk behaviors to pre-treatment levels.

Stigma

From the beginning of MMT, the program has been stigmatized by the belief that methadone treatment merely substitutes one drug for another. This belief blurs the crucial differences between an active heroin addiction and the use of methadone in a maintenance program. Gordis cites methadone maintenance as an example of a soundly researched medical program about which misperceptions and biases have had an adverse impact on implementation (62). Cooper indicates that methadone maintenance has met with limited acceptance by doctors because addiction is not regarded as a legitimate medical condition (63). Misunderstandings about addiction, the role of MMT, and the stigma associated with both may generate counterproductive policies such as excessive regulations and the prescribing of sub-optimal doses for patients. Gordon reported that employers were more sympathetic to active alcoholics than to stabilized methadone patients (64). Programs for alcoholics were available, and even though workers might have been impaired by alcohol, they were referred to treatment programs that were sometimes affiliated with their jobs. Gordon observed that alcoholism is accepted by society, whereas enrollment in methadone treatment leads to social ostracism. Methadone patients, accordingly, are fearful of being suspended, fired, or not hired if their status becomes known to current and potential employers, despite the fact that they are not impaired by methadone maintenance and can perform job tasks for which they are qualified. Joseph reported that stigma pervades the lives of methadone patients, arousing fears about discovery and a need to conceal enrollment in the program from members of their families, friends, employers, and health personnel who treat them (65). Patients have indicated that if they inform people about their enrollment, then routine fatigue might be misinterpreted as narcotization from methadone. Also, communities have refused to allow the construction of methadone treatment centers even though a need for the treatment has been established. Miller, Bayer and Joseph have analyzed news articles, documentaries and journal articles that present methadone maintenance with distortions and biases which add to the stigma and misinformation (65, 66, 67). To fight stigma, discrimination, and questionable regulations, methadone patients have formed advocacy groups, most notably the National Alliance of Methadone Advocates, with affiliations throughout the United States, Europe, and Australia.

Current Problems

In the early 1970s, Gearing noted that patients were being admitted to methadone treatment with a greater prevalence of problems than those admitted in previous years (21): antisocial behavior; increases in polydrug abuse, including cocaine addiction and alcoholism; and life-threatening illnesses such as cancer, neurological problems, heart and lung conditions. In the social realm, Gearing identified the disappearance of the types of jobs that patients were able to obtain in the 1960s, when the program began, and the reluctance of employers to hire methadone patients. These observations were harbingers of the serious social and medical problems that still impact on the patients and the program.

- The HIV/AIDS epidemic within the drug-injecting population had affected a significant proportion of the patients by 1985 (68). Estimates ranged from 5–57% of the clinic population, depending on the location of the clinic and the number of years the patients injected drugs with contaminated injection equipment. By the mid-1980s, AIDS-related illnesses were the major causes of death within the patient population. TB, which was associated with AIDS, became a major public health concern. Therefore, in response to the manifestations of infectious diseases, clinics became centers for detection and treatment of TB and HIV. Coordinators were placed in New York State methadone clinics to educate patients about infectious disease.

- The cocaine/crack epidemic emerged in the early 1980s, creating serious behavior and medical problems, including transmission of syphilis and HIV, in the exchange of sex for drugs (69), and the exposure of neonates to cocaine in utero. Programs responded by creating special therapy groups to reduce the use of cocaine. However, cocaine and crack are still major problems, since there is no proven medication to treat the compulsive user. About 40% of the approximate 41,000 methadone patients in treatment in New York State on 12/31/99 admitted at the time of their admissions to the methadone program that they abused cocaine and crack in addition to heroin (70). The combined injection of heroin and cocaine, known as speedballing, has emerged as a problem among new admissions. However, with extended counseling and treatment, and doses of methadone more than 80 mg/day, speedballing can be reduced (69).

- In the 1990s, hepatitis C was identified at high levels of prevalence within the population of methadone patients who were former drug injectors. Novick (71), Hagan and Des Jarlais (50), and Salsitz et al. (52), all in this issue, indicate that hepatitis C has now become a major health problem among methadone patients.

- In the 1970s, 80s, and 90s, there was erosion of affordable housing, including single occupancy hotels (75). This erosion was accompanied by a change in the job market from relatively unskilled manufacturing and factory jobs to a service economy that demanded education and technical skills. These two trends produced high unemployment rates and homelessness, both of which were reflected in the admission statistics to the program. Currently, about 10% of the patients report upon admission that they are homeless or living as transients; only 20% are employed. When methadone maintenance started in the mid-1960s and 1970s, homelessness was not an issue and a greater proportion, about 33%, of the patients were employed at time of admission.

- Community resistance has prevented the opening of new methadone programs and clinics, thereby limiting the expansion of methadone maintenance. Community resistance is based on complaints of loitering or drug sales by the patients, whether or not these complaints are valid, and the sale and diversion of methadone by unemployed patients around the clinics (65, 71, 72).

- Currently, between 15 and 20% of the admissions to methadone treatment statewide have histories of either past or present mental illness and mental retardation. In addition to methadone maintenance, these patients also need mental health services (70).

Federal Regulation of Methadone

In 1995, the IOM issued a report entitled, "Federal Regulation of Methadone Treatment" (18). The report identified the following three tiers of governmental regulation at the federal level:

- The Department of Health and Human Services (DHHS) is responsible for setting standards concerning the circumstances under which methadone may be used in the treatment of opiate addiction.

- The Food and Drug Administration (FDA), which implements the standards set forth by the DHHS in conjunction with the Substance Abuse and Mental Health Services Administration (SAMHSA).

- Since methadone is a highly controlled substance, it is subject to regulations of the Drug Enforcement Administration (DEA) to prevent diversion.

In addition, state agencies and local (e.g., county or municipal) governments may promulgate their own regulations based on the federal requirements.

Thus, potentially, five tiers of regulation can exist to oversee MMT. The IOM report (18) while acknowledging the benefits of MMT, indicates that federal regulations are hampering the expansion and accessibility of the program. This is summarized in the following statement: "Current policy, in the committee's view, puts too much emphasis on protecting society from methadone, and not enough on protecting society from the epidemics of addiction, violence, and infectious diseases that methadone can help reduce."

The IOM recommended that:

- Regulations be modified to permit greater access to treatment for all opiate-addicted persons.
- Clinical practice should not be arbitrarily restricted.
- Withdrawal from treatment should not be promoted without considering the probability of the patient's relapse after leaving treatment, and patients should be accorded valid reasons and/or hearings, if necessary, in the decision to terminate treatment.
- Dose levels of patients should be determined based on individual patient need.

National Institutes of Health Consensus Statement on Effective Medical Treatment of Opiate Addiction

A consensus statement by the National Institutes of Health (NIH) on the treatment of opiate addiction was released in November of 1998 (23). Some of the conclusions are as follows:

- Opiate dependency is a brain-related medical disorder, which can be treated. (This statement is validated by NIH through an investigation of neurobiological and epidemiological research that has documented the consequences of heroin use and the chronic relapsing nature of opiate dependency irrespective of the ethnicity, cultural background or social class of the patient.)
- Methadone maintenance coupled with relevant social, medical and psychological services has the highest probability of being the most effective of all available treatments for opioid addiction.
- Opiate-dependent persons under legal supervision — probation, parole, in jails and prisons — should have access to MMT. The U.S. Office of National Drug Control Policy and the U.S. Department of Justice should take the necessary steps to implement this recommendation.
- Stigmas and misunderstandings about addiction and methadone treatment are barriers to expanding treatment. Therefore, leadership, both political and medical, is needed to educate the public.
- Current regulations were deemed overly intrusive by the consensus panel. Recommendations included eliminating current FDA regulations and replacing them with accreditation for improving methadone treatment.
- With training of health professionals and guidelines for accreditation replacing regulations, methadone could be prescribed and dispensed in a variety of medical settings outside of the current clinic system, including physicians' offices, primary care centers, and pharmacies.
- Funding for MMT must be increased. Coverage for treatment of opiate addiction should be included in public and private insurance.

As a result of the IOM and NIH reports, it is anticipated that the FDA regulations will be eliminated and replaced by the same accreditation process that hospitals undergo. The authority over the accreditation process will be transferred to the Center for Substance Abuse Treatment (CSAT) of SAMHSA. A major emphasis in this process will be the transfer of selected groups of patients from the clinic system to MMT primary care facilities and the office-based practices of a physician.

Innovations Supported by the New York State Office of Alcoholism and Substance Abuse Services (OASAS)

The New York State OASAS has anticipated several recommendations from the IOM and NIH reports. The programs developed in New York State have served as models for development throughout the country:

- Since 1987, MMT has been available in the New York City jail system in the Key Extended Entry Program (KEEP) and patients are referred from the jail to community programs for continued treatment.

- New York City has had a highly successful program of physicians prescribing methadone maintenance in their office-based practices since 1983. The program is known as Methadone Medical Maintenance. As of this writing, three methadone medical maintenance programs are in operation and a fourth in Buffalo has been approved.

- Methadone maintenance is usually barred from many facilities treating other substance abuse problems, but since 1997, methadone has been available in the OASAS-operated Addiction Treatment Centers, formerly known as Alcohol Treatment Centers.

- OASAS has approved a statewide waiver which allows physicians working in methadone maintenance to prescribe doses of methadone found to be necessary for an individual patient — up to 150 mg/d without state approval and more than 150 mg/d with approval.

- The Lower East Side Service Center, a Manhattan-based drug treatment program licensed by OASAS, developed a program in 1982 integrating MMT within a residential setting. This program is known as the Short Stay Methadone Residence.

- Insight House in Utica, NY, and Horizon Village in Niagara County, NY, are therapeutic communities which have been offering MMT to eligible residents since 1999.

- OASAS was also instrumental in helping skilled nursing facilities with DEA-licensed pharmacies, including those serving AIDS patients, to offer MMT on the premises.

Discussion

Medical studies have shown that methadone maintenance is medically safe and nontoxic, can be used effectively in pregnancy, and does not impair intellectual, cognitive or motor functioning. Methadone maintenance is a corrective, not a curative treatment for heroin addiction. It may be necessary for patients to remain in treatment for indefinite periods of time, possibly for the duration of their lives. However, patients can work in any capacity for which they are trained, live normal lives with their families and, if not infected with HIV or hepatitis C, or afflicted with other potentially fatal illnesses, show improvements in their health status. And if infected, methadone-maintained patients can more easily access medical help than can untreated addicts.

Equally important, large-scale expansion of methadone treatment has been shown to benefit the community, with reduced addiction-related crime, reduced transmission of infectious diseases and reduced addiction-related mortality. With regard to optimum dosage, early studies recommending effective doses in the range of 80 – 120 mg/d and over have been validated in subsequent studies: patients remained longer in treatment and either greatly reduced or eliminated the use of heroin and other drugs. Also, patients maintained at higher doses had significantly less HIV infection than patients maintained on lower doses.

Since the 1970s, methadone programs have been admitting patients with potentially fatal illness (e.g., cancer, drug-resistant TB, AIDS, hepatitis C), polydrug abuse (e.g., cocaine/crack addiction, alcoholism, dependency on other drugs) and mental illness. Furthermore, the homelessness and low rates of employment among the new admissions have created a significant subgroup of destitute patients with serious medical and psychiatric problems, making the delivery of services more challenging for clinics. To address these issues, methadone programs are in the process of developing primary care components and liaisons with social and medical institutions, to create treatment models that address both the addiction issues and co-morbid social and medical conditions.

Stigma and the resulting discrimination appear to be the most powerful social forces preventing the full acceptance of methadone treatment. With a few notable exceptions, media reports have in general distorted methadone treatment, adding to its stigmatization.

Conclusion

The IOM and the NIH have reviewed the issues surrounding MMT. The agencies have concluded that opiate addiction is a medical disorder and that methadone maintenance with relevant ancillary services is the most effective treatment for opiate addiction. Both agencies stressed the need to expand the program to treat the hundreds of thousands of untreated heroin users nationwide. To increase accessibility to treatment, both agencies recommend the expansion of methadone maintenance, the training of more health personnel, the easing of regulations on federal, state and local levels to permit the opening of new programs, and the development of new models of treatment. However, effective medical and political leadership is necessary to reduce the social stigma surrounding addiction and methadone treatment in order to effectively implement these changes.

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The Cost-Effectiveness of Methadone Maintenance

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Abstract

Background: Although methadone maintenance is effective in reducing injection drug use, needle sharing, and the overall mortality associated with opiate abuse, many health plans offer little or no access to methadone, and many methadone providers do not comply with treatment guidelines regarding dose, duration of treatment, or provision of ancillary services. Moral and political judgments have helped shape the U.S. treatment system. Evaluations of methadone cost-effectiveness may play a role in changing public policy.

Methods: Cost-effectiveness analysis is used to compare a change, or changes, in treatment to that of current standard care. The cost of treatment and its effect on outcomes are used to find the incremental cost-effectiveness ratio, and determine whether the change(s) should be adopted. The literature on methadone maintenance is reviewed from an economic perspective, focusing on five policy questions: (1) whether methadone should be a health care benefit; (2) what level of ancillary services is optimal; (3) what methadone dose is appropriate; (4) what length of treatment is appropriate; and (5) whether contingency contracts should be employed.

Results: Expanded access to methadone maintenance has an incremental cost-effectiveness ratio of less than $11,000 per Quality-Adjusted Life Year. This is more cost-effective than many widely used medical therapies, a finding that strongly supports the inclusion of methadone in the formulary of health care plans. Ancillary services have been shown to be an effective part of methadone maintenance therapy, especially during the beginning of a treatment episode, but there is not enough information available to tell whether the optimal amount of services is being used. There is extensive evidence that many treatment programs dispense inadequate doses of methadone. The cost of additional drugs is very small compared to the benefits of an adequate dose. Many methadone programs limit treatment to 6 months or less, but such short episodes are not likely to be cost-effective. The medical model of methadone maintenance may increase the cost-effectiveness of the treatment for long-term patients. Programs that reward patients for negative urinalysis have proven effective at reducing illicit drug use, but their cost-effectiveness will need to be demonstrated before they are widely adopted.

Conclusions: Cost-effectiveness researchers need to measure substance abuse outcomes in terms of Quality-Adjusted Life Years, as this will make their findings more relevant to the development of treatment policy. It will allow different substance abuse treatments to be compared to each other and to medical care interventions.

Key Words: Methadone, cost-benefit analysis, opioid-related

Introduction

Methadone maintenance is an effective treatment for opiate abuse. It reduces injection drug use and needle sharing (1–6) and the overall mortality associated with abuse of opiates by injection (7–9). Unfortunately, most who could benefit from methadone do not receive it. There are between 1 and 1.5 million injection drug users (IDUs) in the U.S. (10–12), between 600,000 and 800,000 of whom are addicted to heroin. There were 179,000 patients enrolled in U.S. methadone treatment programs in 1998 (13).

Many health care payers; including the Medicaid programs of 25 states and the Medicaid managed care programs of an additional 11 states, do not cover methadone maintenance (14). Out-of-pocket payments by patients are an important source of treatment revenue, and failure to pay these costs is an important reason why treatment is discontinued (15). Even when patients are able to enroll in a methadone program, the treatment they receive may not be optimal. Many programs do not follow treatment guidelines regarding length of treatment, provision of psychosocial services, or dose of methadone (16, 17).

Many factors affect access to methadone treatment and the design of treatment programs. Moral and political judgments about opiate dependence have influenced the U.S. treatment system (18). However, emerging literature on the cost-effectiveness of substance abuse treatment may play a role in changing public policy.

Health care payers are increasingly using cost-effectiveness analysis as a tool to decide which medical therapies should be covered by their health care plans. Cost-effectiveness analysis can help determine whether methadone maintenance should be included in health care plans

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and whether changes in methadone treatment add sufficient value to justify their cost. Moreover, such analysis can provide information on whether enhancements such as intense social services and contingency contracts that reward methadone patients with vouchers or cash for adhering to treatment are significantly cost-effective to be adopted.

Complete cost-effectiveness analysis should incorporate the effect of methadone maintenance on related medical care costs. The medical comorbidities associated with opiate addiction include HIV, hepatitis, endocarditis, overdose, soft-tissue infections, and many other diseases (19). These diseases are costly to treat. For example, the lifetime cost of treating HIV is estimated to be $103,552 (1999 dollars) (20). HIV-positive individuals who have not developed AIDS incur higher costs if they are IDUs (21). AIDS patients incur 38% more health care costs, as well as greater long-term care costs (22), if they are IDUs (23).

Methadone maintenance decreases costs incurred by social services agencies and the criminal justice system (24, 25). Public policy makers will be interested in cost-effectiveness analysis that also considers the effect of treatment on social costs such as these.

This paper reviews literature on methadone maintenance treatment from an economic perspective. It describes methods of cost-effectiveness analysis and then addresses the following policy questions: (a) Should methadone maintenance be offered as a benefit of health care plans? (b) What is the appropriate dose of methadone? (c) What psychosocial services should be offered? (d) How long should methadone maintenance treatment continue? (e) Should contingency interventions be adopted? This review not only considers the literature on methadone maintenance treatment that uses economic methods; it also reviews data from observational studies and clinical trials. We then propose hypotheses about the cost-effectiveness of proposed changes to methadone maintenance treatment.

Methods of Cost-Effectiveness Analysis

Cost-effectiveness analysis is a tool used to aid in making decisions as to what care should be offered. It is a method of comparing the cost and effectiveness of two or more alternatives. Such comparisons are most useful when one of the alternatives being considered is standard care, since this allows the decision maker to consider whether an innovation is better than the status quo. The figure is a graphical representation of four hypothetical treatments, plotted according to cost and outcome. Note that any of the points in the figure might be the status quo.

When one of the alternatives saves costs and improves outcomes, it is favored; this principle is called "dominance." In the graph, alternative A is always preferred over alternative C, since it yields better outcomes at lower cost.

When one of the alternatives is more costly and yields better outcomes, dominance provides no guidance. For example, intervention B is more effective than intervention A, and it is more costly. Whether intervention B is acceptable depends on whether the decision maker believes that the additional effectiveness it yields justifies its additional cost; it is a value decision. Cost-effectiveness analysis provides a formal means of making this decision.

First, the incremental cost-effectiveness ratio is found. This ratio is simply the change in cost divided by the change in outcome. Note that to find this ratio, a single-dimensional effectiveness measure is required. The ratio is then evaluated against a threshold criterion for what constitutes a cost-effective intervention.

To facilitate the comparison of different interventions, a standard method of cost-effectiveness analysis was developed by a task force of experts organized by the U.S. Public Health Service (PHS) (26). The Task Force recommended that cost-effectiveness studies use the Quality-Adjusted Life Year (QALY) as the outcome measure, acknowledging the widespread use of this measure in cost-effectiveness studies of health care interventions.

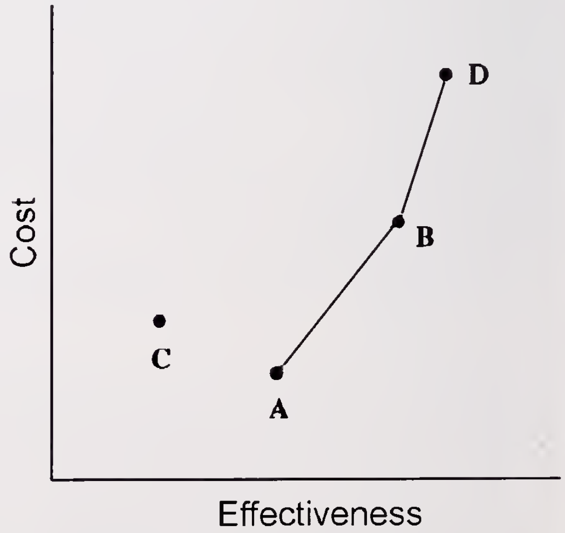

Figure. Comparison of the cost and effectiveness of four hypothetical interventions.

The QALY is an outcome measure that reflects both the quantity and quality of life (27). Quality-of-life adjustments are based on patient or societal ratings of the quality of life associated with different health states. The ratings, also known as "preferences" or "utilities," have a scale of zero (representing death) to one (representing perfect health). There are several methods for obtaining these ratings. The Time-Trade-Off method asks the individual doing the rating how much healthy life they are willing to give up to be cured of the condition. The Standard Gamble method asks them how much of a risk of death they are willing to incur in order to be cured of the condition. There has been widespread use of preference assessments in medical care, but they have not yet been used to rate the quality of life associated with substance abuse disorders.

The cost-effectiveness ratio represents a measure of how efficiently the proposed intervention can produce an additional QALY. By using this standard method, the cost-effectiveness of alternative innovations can be compared, helping health-care payers decide which changes they should adopt. The PHS Task Force did not recommend a standard of what constitutes a cost-effective intervention, that is, how low the cost-effectiveness ratio must be for an intervention to be adopted. Others have observed that the U.S. health care system adopts treatments that cost less than $50,000 per quality-adjusted life year (28).

Finally, the figure also illustrates the concept of diminishing marginal returns. Intervention D is more costly than intervention B, and more effective. The slope of the line connecting B to D is greater than the slope of the line connecting A to B. This means that the incremental cost-effectiveness ratio is greater. This illustrates a general economic law of diminishing marginal returns. Adding additional resources does not necessarily result in a proportionate increase in production; with very high levels of resource use, the production process becomes increasingly inefficient at producing the desired outcome. The goal of the decision maker is to adopt all interventions that represent efficient ways of producing QALYs and to disapprove of interventions with ratios that are too high.

The PHS Task Force made other recommendations on how a cost-effectiveness analysis should be conducted. Among these was the recommendation that society's perspective be adopted, so that all effects of an intervention on cost will be included. To follow this recommendation, substance-abuse treatment studies should include the effect of intervention on costs of medical care, patient-incurred costs, and costs of public agencies such as social welfare and criminal justice agencies.

With this background, we now examine how cost-effectiveness analysis can help decision makers decide whether methadone maintenance should be included in the scope of benefits of health care plans, what ancillary services, dose, and length of treatment are optimal, and whether contingency contracts are an appropriate part of treatment.

Should Methadone Maintenance Treatment Be Offered as a Benefit of Health Care Plans?

Methadone maintenance treatment is not covered as a benefit by many private insurers and state Medicaid programs (14). Recent studies suggest that methadone maintenance treatment should be included in health plans because it is cost-effective.

The cost-effectiveness of methadone maintenance was estimated with a simple mortality model. Providing access to methadone maintenance had an incremental cost-effectiveness ratio of $5,915 per life-year (29). This model estimated the effect of expanded methadone access using the change in mortality rates of IDUs after Sweden imposed a moratorium on new methadone enrollment. The model did not consider the effect of methadone treatment on health care costs or on quality of life.

More recent work has considered not only mortality, but also quality of life and the transmission of HIV, and the effect of methadone treatment on medical care costs (30). Expansion of methadone treatment was estimated to have a cost-effectiveness ratio of between $8,200 and $10,900 per QALY, depending on the prevalence of HIV in the community. A wide range of modeling assumptions found that most of the HIV infections that were prevented would be among IDUs, but because of their short life expectancy, most of the gain in quality-adjusted life years would be realized by members of the general population. In addition, this paper found that an intervention that was twice as costly and half as effective as methadone maintenance would still be judged as cost-effective.

Both studies were limited to the health care payer's perspective. They did not include costs incurred by patients or non-health care costs of government agencies. Some studies have found that reduction of public agency costs brought about by treatment is substantial (24, 25). If these additional costs were considered, they would have offset some of the treatment costs, lowering the cost-effectiveness ratio.

These cost-effectiveness studies found that, by the standards used to judge medical care interventions, methadone maintenance is highly cost-effective. For example, its cost-effectiveness ratio is lower than that of many HIV interventions. Prophylaxis for opportunistic infections of AIDS has much higher ratios: $16,000 per QALY to prevent *Pneumocystis carinii* pneumonia (31), $35,000–74,000 for *Mycobacterium avium* complex, and more than $160,000 per QALY to prevent infection by cytomegalovirus (32, 33). Chemoprophylaxis for high-risk occupational exposure to HIV has a ratio of $37,000 per QALY (34). Access to methadone maintenance has a cost-effectiveness ratio that is similar to that of other HIV prevention programs, including chemoprophylaxis for high-risk sexual exposure, $6,300/QALY (35), and a program to increase condom use among high-risk women, $2,000/QALY (36).

Proponents of expanded methadone maintenance treatment should be encouraged by the finding that it is a highly cost-effective treatment. If they wish to apply cost-effectiveness rules to demonstrate that methadone maintenance treatment should be offered, they must also consider what cost-effectiveness analysis has to say about the design of treatment programs and the interventions that have been proposed to improve treatment effectiveness.

How Much Ancillary Service Should Be Offered with Methadone Maintenance Treatment?

There is substantial evidence that methadone maintenance is more effective when ancillary services, such as counseling, social services, and medical care, are offered along with methadone. According to a study of 17 clinics, patients in programs that provided more frequent counseling contacts were less likely to use illicit drugs (37). According to another study, patients were retained longer in programs that provided high-quality social services (38). And cognitive-behavioral interventions have been found to reduce risky injection practices (39) and cocaine use (40).

Although the data referred to above is impressive, cost-effectiveness analysis is needed to determine whether the additional benefit of different ancillary services justifies their costs. Few studies have examined this question. A randomized trial compared a day-treatment program that provided 25 hours a week of specialized services to a standard methadone program that included only a few enhancements. This trial found that the day-treatment program was three times more costly, but that there was no significant difference in patients' use of illicit drugs (6). This result suggests that, according to the dominance principle, the day-treatment program should not be adopted — since it is more costly and not more effective. However, the study has some limitations. The intervention was delivered over a limited time period and the alternative treatment was not standard care; the study did not report the statistical significance of the dominance finding; day-treatment patients were slightly less likely to use drugs, and the study may simply have been too small to detect an effect that was significant. There are a variety of statistical methods that can be used to determine the significance of cost-effectiveness findings (41).

Another randomized trial found that methadone with standard counseling yielded better outcomes than methadone alone, and that an enhanced set of counseling and medical services was even more effective (42). A subsequent analysis considered the cost-effectiveness implications of this trial (43). This analysis reported a cost-effectiveness ratio in terms of the annual cost per abstinent patient, and concluded that the highest level of services was not cost-effective. There are two problems with using abstinence as the outcome measure. This outcome measure assumes that there is no value in treatment effects other than total abstinence. Other outcomes, such as reduction in the use of opiates and the rate of unsafe injection practices, should be considered. Another problem is that we do not know how much society is willing to pay for a year of abstinence from opiates. Had this study used QALY as the outcome measure, we could have compared the incremental cost-effectiveness ratios to the ratios found for other types of health care.

Research on the impact of ancillary services on methadone effectiveness suggests a number of areas where cost-effectiveness research is needed. The Treatment Outcome Prospective Study (TOPS) found that patients were retained longer when specialized professionals were involved in diagnosis and development of treatment plans (44). A cost-effectiveness study is needed to determine whether using a different mix of treatment professionals will enhance the cost-effectiveness of methadone maintenance. This is a compelling area for research, since staffing costs account for most of the cost of treatment.

The effectiveness of psychosocial services may depend on when they are offered. Services offered at the beginning of a treatment episode may be especially cost-effective. One of the studies referred to earlier (38) found that if the treatment program provided high quality social services during the first month of treatment, patients were three times as likely to be retained in treatment for at least a year. Patients in the 21 methadone clinics studied in the TOPS study were more likely to remain in treatment if they received more medical, psychosocial, and financial services during the first three months of treatment (44).

Services offered later in a treatment episode may not be as cost-effective. A study of medical maintenance found that about 83% of eligible long-term methadone patients were treated successfully in programs that involved monthly physician visits, dispensing a month's supply of take-home medication, and no ongoing counseling other than discussions with the treating physician about personal and medical problems (45). Taken together, these studies suggest that the marginal value of social services may decline during the later part of a treatment episode. Studies are needed to determine the optimal timing of psychosocial services and to learn whether services provided later in a treatment episode are sufficiently cost-effective to be justified.

A randomized trial found that individuals waiting to enter comprehensive methadone treatment did better if they received methadone with minimal services, rather than no treatment at all. Patients who received this interim treatment were less likely to use illicit opiates and had better long-term outcomes (46). It would be worthwhile to learn the incremental cost-effectiveness of interim treatment compared to standard therapy that includes psychosocial services. If the incremental cost-effectiveness of the additional services is not sufficiently large, then perhaps they are not cost-effective. In other words, if there are too few resources to treat all those who wish to enter methadone treatment slots, it is possible that resources could be better used to provide methadone to a greater number of individuals, but with minimal psychosocial services.

What Is the Proper Dose of Methadone?

There is extensive literature documenting the greater effectiveness of higher doses of methadone. Double-blind, randomized, controlled trials have found that patients who are given higher methadone doses are retained longer in treatment and are less likely to provide opiate-positive urine samples. The trials have demonstrated that a daily dose of 50–60 mg is superior to 20 mg (47, 48) and that a dose of 80–100 mg is superior to 40–50 mg (49, 50). Observational studies have also found that patients were retained longer if they received a higher dose (44–51), and that they also had fewer opiate-positive urine samples (52). One study reported that the relative odds of patients using heroin while in treatment were reduced by 2% for every 1 mg increase in the daily dose of methadone (53). Other studies have found that patients do better in treatment programs that use higher doses (54).

There is growing evidence that different patients require substantially different doses of methadone, and that some patients require doses well in excess of 100 mg per day (55). Treatment for one group of patients was improved when their daily dose was increased to a range of between 110 and 780 mg (56). Cost-effectiveness analysis will help to determine if high-dose treatments result in additional costs for such items as additional medical evaluation or additional testing of serum methadone levels.

Programs that provide higher doses have other characteristics that may affect the cost of an episode of care. High-dose programs have less restrictive rules and the intent of retaining patients longer (51). Treatment programs that have a higher upper limit on dose are more likely to have patients who are aware of their doses, allow them to influence their doses, and grant take-home privileges (17). These other characteristics are also associated with improved treatment efficacy. Patients are more likely to be retained in treatment when dosing policy is flexible (57) and when they are informed of the doses that they receive (58).

The efficacy of higher doses may be greater when administered early in the treatment episode. One study found that patients were less likely to provide opiate-positive urine specimens if they received higher methadone doses during the first 5 months of treatment; this measure of illicit drug use was not affected by the dosages received later in treatment (59). Another study found that the maximum dose in the first 120 days of treatment predicted subsequent retention (51). If higher doses result in higher costs, then this strategy may be more cost-effective if it is targeted to the early months of treatment.

While high doses, flexible-dosing policies, and informing patients of their dose are effective, such treatment strategies are not uniformly applied. A survey of 172 U.S. methadone maintenance programs found that nearly one-fourth of methadone patients received a daily dose of less than 40 mg per day, a level that most researchers regard as too low to be effective (17). This same survey found that one-third of program patients were not well-informed of their doses, and that most patients had little or no influence over the doses they received.

Methadone is inexpensive. The cost of methadone, at less than a dollar a dose, makes up only a small part of the total treatment cost. Specialized dispensing adds to this cost, but the cost would be minimally affected by increasing the dose, adopting flexible dosing policies, or tailoring the dose so it is adequate for the patient's need. Such policies represent low-cost interventions; given their benefits, they are likely to be very cost-effective. A complete analysis requires inclusion of any additional costs associated with high doses, such as increased medical monitoring of patients or the risk associated with higher doses. Current studies suggest that such costs would be relatively small compared to the consequences of continued injection drug use that occurs when doses are too low.

How Long Should Treatment Continue?

There is considerable evidence that greater time in methadone treatment is associated with better outcomes. Methadone patients who were in treatment longer used illicit drugs less frequently and were involved in fewer criminal activities, according to the one-year follow-up interviews conducted by the Drug Abuse Reporting Program (DARP) (60) and TOPS (61) studies, and in the six-year follow-up interviews of DARP subjects (62). Arbitrary termination of methadone is associated with poor outcomes. A study of the closure of a California methadone program found that patients who continued their methadone treatment in a different program had better outcomes than those who did not continue in any program at all (63).

These observational studies were not randomized tests of the effect of longer treatment and thus cannot prove that longer treatment causes better outcomes. Although the studies had controls for the effect of patient characteristics, unmeasured patient characteristics that predict good treatment outcomes may also be associated with longer stays.

A causal relationship between treatment length and outcomes is suggested by studies that have found that programs that limit treatment length have poorer outcomes. Ball and Ross (16) found that patients had better outcomes when enrolled in programs that had long-term maintenance on methadone as their treatment goal; patients in abstinence-oriented programs did more poorly. Other studies (51 – 54) found that patients in programs that limit treatment length have poorer outcomes than those in programs without time limits. This result, however, is confounded by the lower doses used in the limited-length programs.

Long-term maintenance with methadone is advocated because efforts at detoxification are usually not successful. Long-term follow-up studies have found that patients who terminate methadone, even when detoxification is approved by program staff, have low rates of abstinence (64 – 66).

The efficacy of longer treatment has been demonstrated in at least one randomized clinical trial. Standard methadone care was compared to a 180-day detoxification program with enhanced services; despite the enhancements, the shorter program was less effective (67).

Although there is strong evidence that longer treatment is more effective, limits are often placed on the length of time patients may receive methadone. A survey of U.S. treatment programs found that 32% of their patients were encouraged to detoxify from methadone within the first 6 months of their treatment (17). Many health plans specify a maximum number of weeks of methadone maintenance that will be covered (14).

It is not known whether current limits on treatment length are based on cost-effectiveness considerations. Treatment length may be limited because of the social stigma associated with methadone treatment, moral judgments made about opioid dependence, and the belief by some that abstinence is the only acceptable treatment outcome. There are economic incentives to limit treatment length. The limits on methadone treatment specified by many private insurance plans have shifted treatment costs to the public sector (14).

A National Institutes of Health panel on methadone treatment recommended that "most, if not all, patients require continuous treatment [with methadone] for many years, and perhaps for life" (68). Opioid dependence is a chronic condition for which many patients cannot be cured; thus they require indefinite treatment, much as insulin is required by diabetics.

The six-year follow-up of DARP data found that patients who had received fewer than 90 days of treatment did not do better than patients who were never treated (62). Very short treatments have a cost; if they yield no benefit, the dominance principle holds that they are not cost-effective.

A medical model of maintenance therapy has been proposed for long-term methadone patients.

Pilot programs have enrolled longstanding patients with good records of compliance. The patients make monthly visits to a primary care physician and receive a month's supply of medication. Outcomes appear to be at least as good as those achieved in methadone treatment programs (45, 69, 70). If medical maintenance lowers the cost of treating long-term patients without compromising the outcomes, it will strongly dominate standard care.

Should Contingency Contracting Be Employed?

Most methadone patients are required to provide regular urine samples that are screened for illicit drugs. The value of this monitoring is not precisely known. It appears to have little value if the information is not used to guide care. When patients from 5 clinics were randomized to either a monitored or unmonitored group, surprise urinalysis found no statistically significant difference in the rate of illicit drug use (71). Patients assigned to the monitored group had fewer positive urinalyses, but they were also more likely to drop out of treatment. The authors of this report note that a system of monitoring urine samples may result in 5–11% fewer drug-positive urine specimens, but they were uncertain about whether the cost was worth the result.

Other trials have undertaken specific interventions that are contingent on the results of urine monitoring. Patients agree to contracts that specify the consequences of a positive urinalysis. It may affect their tenure in treatment, the dose they receive, whether they are granted take-home privileges, or whether they receive incentives such as vouchers or cash credits.

A randomized trial evaluated a structured treatment program that required patients to provide negative urine specimens for at least one month out of every four, or else be discharged (72). This intervention resulted in significantly less drug use and greater retention.

Methadone patients reduced their use of illicit opiates when their dose was changed as a result of a positive urinalysis (73). Patients reduced their drug use regardless of whether the dose was increased or decreased; however, the patients who were given a decreased dose were more likely to drop out of treatment.

A recent trial gave patients the choice between a take-home dose or a $25 voucher as their reward for a negative urinalysis (74). This intervention reduced use of opiates and cocaine. Cost-effectiveness research is needed to determine if the improvement in outcomes achieved by these interventions justifies their cost. Economic analysis will be especially important in justifying the use of contingent rewards.

A cost-effectiveness study examined a trial in a 180-day methadone detoxification program that rewarded negative urinalyses with cash credits (75). Patients who were randomized to the contingent rewards group were more likely to provide urine and breath samples that were free of drugs and alcohol. The contingency payments were a small part of the total cost of treatment. The contingent rewards group had higher treatment costs and incurred fewer health care costs, suggesting that the extra treatment costs are substantially offset by reductions in health care cost; however, the differences were not statistically significant. The authors report a cost-effectiveness ratio of $17.27 per 1% increase in the individuals whose samples were free of illicit substances. This ratio excludes the effect of treatment on health care costs. The use of abstinence as the outcome raises two problems. First, it does not value reductions in substance use that do not involve abstinence. Second, since the value of achieving abstinence has not been established, it is not known how low the ratio must be for the intervention to be considered cost-effective.

Discussion

Cost-effectiveness methods developed for the evaluation of health care have determined that expansion of methadone maintenance treatment capacity has a cost-effectiveness ratio that is lower than many widely used medical care interventions (29, 30). An important benefit of the expansion of methadone treatment capacity is a reduction in the transmission of HIV, an outcome that benefits the general population. This benefit is so substantial that expansion of methadone treatment is cost-effective regardless of what assumptions are made about the effect of opiate dependence or methadone prescription on quality of life (30).

For cost-effectiveness methods to be more widely applied to the substance abuse treatment system, however, information on quality-of-life adjustments will be needed. A key research gap is the need for preference assessments, to allow cost-effectiveness researchers to measure substance abuse outcomes in terms of Quality-Adjusted Life Years.

Because cost-effectiveness analysis is a tool for assigning community health care resources, community ratings should be used to assign quality adjustments to health states (26). Quality adjustments are needed to reflect the quality of life of untreated addicts and methadone maintenance patients. These adjustments will need to reflect the effect of co-morbidities, including HIV infection and AIDS.

In the absence of this information, cost-effectiveness analysts will be able to make only limited progress. They will be able to apply the dominance principle, recommending adoption of interventions that save costs and improve outcomes. Unfortunately, dominance is an inadequate tool for the evaluation of most policies. Dominance does not tell whether to adopt a policy that would both increase costs and improve outcomes (such as proposed treatment enhancements). It also does not help when choosing a policy designed to save costs at the expense of worsening outcomes (e.g., policies that limit dose, counseling services, or treatment length).

When dominance does not apply, the decision maker must evaluate the incremental cost-effectiveness ratio. Most economic evaluations of methadone maintenance have calculated this ratio using natural units of outcome, such as number of weeks with negative urinalysis, or the number of years of abstinence from illicit drugs. It is difficult to judge ratios that use this type of outcome measure. For example, no one has determined how much society should pay to achieve an abstinent year of life. In addition, such measures do not reflect the multi-dimensional nature of outcomes, such as reduced medical co-morbidities, or the effect of the treatment itself on the quality of life.

Incremental cost-effectiveness ratios that use QALYs as the outcome can be compared to the ratios found in other studies, and to the $50,000 per QALY threshold that has become the de facto standard for the U.S. health care system. The promise of this approach is that it will optimize the use of health care resources, maximizing the total number of QALYs that can be achieved with available health care resources. This promise can be achieved only if quality adjustments are developed that accurately reflect the value that society places on life spent with opioid disorders. These adjustments are needed for individuals with untreated opioid dependence and those in methadone maintenance.

Policy makers may be tempted to incorporate lower social preferences for health states involving illicit injection of drugs, by applying stricter criteria for cost-effectiveness, that is, by adopting a threshold that is higher than $50,000 per QALY. This would be inappropriate; quality adjustments are the way to incorporate these social preferences. A higher threshold would also undervalue the benefit that the non-drug-using population receives from maintenance treatment via reduced spread of HIV.

It must be conceded that cost-effectiveness considerations are not the only factors that shape methadone treatment policies. Untreated IDUs and methadone patients may be seen as less deserving due to the social stigma associated with drug use. Decision makers are influenced by philosophical and moral opposition to opiate substitution therapy. Practices which are known to be ineffective, including inadequate doses and limits on treatment, are still widely employed.

Economic analysts face a daunting challenge. They must find the effect of treatment on cost and outcomes, including the social valuation for these health states. They must also include the dynamic effect of treatment on the spread of communicable diseases, and on social service and criminal justice systems. If this can be accomplished, then improved cost-effectiveness analysis will allow treatment for opioid dependence to be compared to other health care interventions. A likely result is that they will find that funds currently used for health care may be more cost-effectively applied to methadone treatment of opioid dependence. The stigma associated with opiate dependence, however, may prevent policy makers from treating methadone on a parity with other health care interventions.

Even if policy makers cannot regard treatment of opiate addiction on the same level as other health care interventions, cost-effectiveness analysis can still play a role in determining the best use of treatment resources. If all substance-abuse cost-effectiveness studies included the QALY among the outcomes they measure, then decision makers would be able to compare interventions and adopt policies that maximize QALYs among those who seek treatment for opiate addiction.

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Neurobiology of Addictive Behaviors and Its Relationship to Methadone Maintenance

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Abstract

Scientific information about the neurobiology of addictive behaviors provides an increasingly important rationale to support opioid agonist pharmacotherapy, primarily methadone maintenance treatment, for long-term heroin addiction. In late 1963 and 1964, the first research was performed at The Rockefeller Institute for Medical Research by Dole, Nyswander, and Kreek in an attempt to develop a new pharmacotherapy for opiate addiction. The hypothesis underlying that research was that heroin addiction was a disease. However, the evidence for heroin addiction being a disease was based primarily on clinical anecdotes and the natural history of opiate addiction. Until then chronic addiction was managed primarily using abstinence-based, medication-free behavioral approaches. Such approaches were uniformly successful in only a small percent of long-term heroin addicts. Subsequent research, both clinical research as well as laboratory-based research, using a variety of appropriate animal models as well as *in vitro* techniques, has shown that drugs of abuse in general, and specifically the short-acting opiates, such as heroin, may profoundly alter molecular and neurochemical indices, and thus physiologic functions. Also, research has shown that after chronic exposure to a short-acting opiate, these alterations may be persistent, or even permanent, and may contribute directly to the perpetuation of self-administration of opiates, and even the return to opiate use after achieving a drug-free and medication-free state. There is ample evidence now that disruption of several components of the endogenous opioid system, ranging from changes in gene expression to changes in behavior, may occur during cycles of short-acting opiate abuse. Also, there are very convincing studies that suggest that stress responsivity is profoundly altered by chronic abuse of short-acting opiates including: documentation of atypical hypo-responsivity to stressors during cycles of heroin addiction; evidence of sustained hyper-responsivity to stressors in the medication-free, illicit-opiate-free state; and in contrast, normalization of stress responsivity, as reflected by the hypothalamic-pituitary-adrenal axis function in long-term, methadone-maintained patients. Thus, both laboratory and clinical research studies provide firm documentation that the disruption of physiologic, as well as behavioral, functions occurs during chronic administration of short-acting opiates. Also, there is research evidence of an epidemiologic, and more recently of a molecular genetics type, that a genetic vulnerability to develop addictions in general, and opiate addiction specifically, may exist, and that early environmental factors may alter physiology to enhance vulnerability to develop opiate addiction when self-exposed.

Key Words: Heroin, methadone, heroin addiction, methadone maintenance, neurobiology of addiction.

THE INAPPROPRIATE USE of mood-altering drugs transcends the medical arena, and the health costs associated with such use are enormous. Most important, it is the physician who is often the first person to have an opportunity to identify individuals who either have the potential to become drug-dependent or are currently using mood-altering substances. Unfortunately, the conclusion often made by those devoted to the study of addictive behaviors is that physicians, who have been trained to be critical thinkers, lose this ability when dealing with patients who are addicted. Too many physicians share the perception that drug dependence, once developed, is primarily a character defect associated with criminal behavior, which might be best managed outside of the medical realm. In short, drug dependency is often perceived as a socioeconomic or psychosocial, rather than a medical, problem.

There is no question that the sociological, economic, and psychological factors leading to inappropriate use of mood-altering drugs are exceptionally important, as is the need for increased funding to prevent such use. However, recent evidence unequivocally establishes the existence of neurobiological determinants of both initial and especially continuing drug use. The initiation of drug use is a voluntary, self-willed action. Nonetheless, once this use continues, depending on the specific drug, considerable change occurs in the brain that, unless understood and addressed, makes it quite difficult, though obviously not impossible, to provide effective treatment.

As noted by Gardner (1), with the exception of hallucinogens, laboratory animals will voluntarily self-administer mood-altering substances commonly used inappropriately by humans. In addition, with respect to such drugs as cocaine,

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animals will continue to administer these substances, often choosing them over food and water. Although there are distinct differences between euphoria- and/or dependence-producing drugs (Table 1), with the inability of drugs within one group to adequately relieve withdrawal or "craving" for drugs in other groups, all of these agents have one thing in common: they enhance the activity of specific neurobiological circuits. These circuits are commonly described as the "brain reward system."

It is generally believed that the more efficacious the drug is at rapidly producing its pharmacological actions at these sites, the greater its potential for addiction. The actual molecular sites of action of many of these drugs have been well categorized. Through imaging, microdialysis and quantitative autoradiography, as well as other techniques, including genetic cloning, many of these initial sites of drug action have been well established, as have the involved neurotransmitters, or neuropeptides. The effects of these substances of abuse on the reward system of the brain have been able to explain, in part: the clinical phenomena of the pleasure often associated with use of these drugs; the persistent craving that causes the chronic drug user to continue taking the drug; and some of the reasons for both early and late physiological syndromes of withdrawal when specific drugs, such as opiates or alcohol, are abruptly discontinued (Table 2).

TABLE 1
Dependence-Producing Drugs

Group	Examples
Alcohol — Sedatives — Hypnotics — Minor Tranquilizers	Alcohol, barbiturates, chloral hydrate, meprobamate, benzodiazepines
Hallucinogens	Lysergic acid and hallucinogenic amphetamines, mescaline, peyote, khat
Marijuana	Marijuana
Opiates and Opioids	Agonists: morphine, opium, heroin, codeine, meperidine, methadone Partial agonist: buprenorphine Agonist-antagonists: butorphanol tartrate, pentazocine
Stimulants	Amphetamines, cocaine, methylphenidate, weight-reducing drugs
Volatile Solvents	Glues, some cleaning fluids

TABLE 2
Why People Use Mood-Altering Drugs

Reason	Site
Euphoria (Pleasure)	Nucleus accumbens (NAc) Ventral tegmental area (VTA)
Fear of Withdrawal	Locus ceruleus
Drug Craving	Multiple brain sites

Neurotransmitters and Opioid Receptors

The most prominent neurotransmitters and neuropeptides in this process are dopamine, serotonin, glutamate, gamma-aminobutyric acid, and the endorphins (or endogenous opioids) (2–4). Dopamine is credited with playing the primary role in producing most of the euphoria seen with cocaine, nicotine, alcohol, and other stimulants, and is known to contribute to the positive reinforcing effects of heroin and other opiates (4–6). The intensity of euphoria expressed with cocaine has been shown in one study to be proportional to the percentage of dopamine transporters blocked by the drug (7). Rapidly decreasing levels of dopamine following stimulant use are also believed to be responsible for the "crash" observed in outpatient, but not in stress-minimized, inpatient settings when these drugs are discontinued. Very recently, studies were conducted in a molecularly altered "transgenic" mouse model in which the dopamine transporter gene had been deleted (a "knock-out" model). A situation was thus created in which cocaine could not cause increases in extracellular fluid levels of dopamine by blocking the transporter; this in turn removed the putative "rewarding" effect of dopamine surges. These animals were found to self-administer cocaine as readily as the "wild type" mice with intact dopamine transporters (8).

One major type of opioid receptor, namely the mu receptors, has been shown to be responsible for the primary action, including the euphoria experienced by many, but not all, when opioids such as heroin are self-administered. Correspondingly, it is felt that the kappa opioid receptor is responsible for dysphoria, rather than euphoria, and may play a role in opioid withdrawal, although recent studies have shown that natural kappa receptor-directed ligands, the dynorphins, do not cause dysphoria and may augment, not oppose, mu receptor-directed events (9–11). Endorphins, dynorphins, and enkephalins, in response to other drugs such as alcohol and stimulants, are believed to play a role in drug-rewarding effects and also dependence, including alcohol dependence, when this occurs. This phenomenon may explain the observed benefit of naltrexone in decreasing the craving for alcohol.

Cells in the locus ceruleus that secrete norepinephrine have been demonstrated to be responsible for part of the withdrawal phenomena seen with sudden discontinuation of opioids, which results in an outpouring of norepinephrine. However, this "noradrenergic cascade" does not explain many of the acute and subacute phenomena of withdrawal, or any of the signs and symptoms of protracted abstinences. Similarly, serotonin (5-HT) has been related not only to impulsiveness and appetite, but also to dependence and craving. With respect to signal transduction, while opiates acutely inhibit the cyclic adenosine 3'5' monophosphate (cAMP) pathway at time of administration, chronic use results in an upregulation of the cAMP pathway. Abrupt cessation of opiate use leaves an upregulated, unopposed pathway, which in the locus ceruleus results in an increased firing of these cells, and withdrawal (4, 12). There is no question that as neuroscience continues to advance, additional neurotransmitters and receptor sites will be identified, and the understanding of molecular and cellular bases of addiction will become increasingly clear.

The Role of Pharmacokinetics

Parallel to the advances in neurobiology, continued work on the pharmacokinetics of drugs of abuse has helped explain the clinical phenomenon with respect to choice of drugs of abuse. As reviewed by Nutt and Uhl et al. (3, 5), the goal of the drug user is to increase the rate of delivery of the drug to the brain. This explains why a heroin user may progress from smoking heroin, to snorting and then to injecting heroin intravenously. Similarly, cocaine use provides little immediate effect when coca leaves are chewed, but considerable euphoria when freebase "crack" cocaine is smoked or when cocaine is injected intravenously. An understanding of the pharmacokinetics of the euphoria produced by such drugs, especially heroin, which have a very rapid onset and short duration of action, becomes essential when discussing the concept of maintenance for opioid dependency and in understanding the appropriate drugs to use in the pharmacologic therapy for the addictions (13). For example, a drug such as methadone has a very slow onset and long duration of action. It thus occupies the opioid receptors much more slowly than does heroin, and it also provides a sustained perfusion of agonist, allowing the brain to compensate for the deleterious effects of the short-acting, rapid onset and offset of heroin, and it does so without producing euphoria.

The Tolerance Threshold

Equally important is an understanding of the clinical phenomena of euphoria, tolerance, and withdrawal with respect to the opioids. It has been demonstrated repeatedly that an individual dependent on an opioid to which he/she has become tolerant has developed a tolerance threshold that, if exceeded too rapidly or too far, can produce euphoria and, if very rapidly and very far, an overdose. Correspondingly, if this tolerance threshold is diminished too rapidly, withdrawal can occur.

However, when an individual is at his/her tolerance threshold to an opioid, normal cognitive and motor functions are maintained and, unless an opioid antagonist is administered to produce withdrawal, it is quite difficult, if not impossible, to determine that the individual is taking an opioid (14–16). This phenomenon explains why individuals with chronic pain syndromes who are maintained on opioids at just above the tolerance threshold, and at a level that relieves the pain but does not cause euphoria, function quite normally, and why individuals on long-acting opioid agonist maintenance therapy for opiate (primarily heroin) addiction with an appropriate agent (e.g., methadone or l-alpha-acetylmethadol) can lead productive and fruitful lives without any long-term risks from such therapy. Failure to understand this not only has resulted in the concept of maintenance therapy being derided and often rejected by those in the health professions but, equally important, it has resulted in patients in chronic pain suffering needlessly.

Heroin Addiction

Keeping this in mind, it is now appropriate to review the course of addiction of a person who becomes dependent on heroin. Since heroin is a relatively short-acting drug and the initial goal is to achieve euphoria, it is necessary to inject the drug several times a day. Each time the drug is injected, the heroin rapidly occupies the opiate receptors and produces its effects. However, with repeated injections, tolerance does develop. Since the goal is euphoria (a "high"), the individual self-administers a progressively larger quantity of heroin. As a result, the heroin user is rarely normal (in a "straight state") either physiologically or behaviorally. Dole et al. (14), describe the user as euphoric when "high." This state is followed by sedation and withdrawal signs and symptoms which render the individual incapable of functioning. When the "high" dissipates and the heroin level starts to drop below the tolerance threshold, withdrawal develops, associated with a "drug craving" to relieve the symptoms of anxiety, tremors, perspiration, muscle and bone pains, and nausea that comprise withdrawal. Drug craving also persists long after the acute withdrawal symptoms have dissipated in persons who attempt abrupt discontinuation of use. In fact, such drug hunger persists in persons after detoxification, regardless of the technique used (16).

It can therefore be seen that chronic use of short-acting opioids such as heroin is responsible for alterations of neurobiological systems, which in turn are responsible for both euphoria and withdrawal symptoms (13, 14). It has been demonstrated by Kreek (15, 16) that such alterations persist even following complete withdrawal of the opioid, clinically manifested by the persistent drug craving considered responsible for the high relapse rate seen in individuals who have been detoxified from heroin (15, 16). This observation has led to the hypothesis that these alterations in neurobiology and physiology, caused by chronic, long-term use of a short-acting opioid drug, may result in persistent craving and drug-seeking behavior (15, 16). In no way does this hypothesis negate the beneficial effects that may accrue from social rehabilitation, psychological counseling, and behavioral modification; rather it supports the now proven therapeutic approaches combining appropriate pharmacotherapy, using a mu opioid receptor agonist, along with counseling, and behavioral and other medical care as needed. This hypothesis also does not address the question as to why a person would initiate heroin use in the first place, although a preexisting vulnerability to develop addiction after self-exposure may exist due to genetic and environmental factors. However, it does explain why in many individuals, such rehabilitative efforts without concomitant pharmacotherapy, although their efforts are quite appropriate and intensive, may not be sufficient to maintain a state of abstinence from illicit use of drugs.

Indeed, in a laboratory model, it has been shown that withdrawal symptoms can be produced in an animal following exposure to a conditioned stimulus, if it had been previously dependent upon opioids, but maintained in a drug-free state for months; when the animal had been dependent on opioids and was given an antagonist drug, the same situation produced withdrawal (17). The human correlate of this is the former heroin addict, drug free for a long period, suddenly feeling a craving to inject heroin when entering an environment where he/she had previously taken heroin.

Maintenance Therapy

If one accepts the neurobiological explanations for drug dependence, as well as the observation that persistent neurobiological abnormalities can be demonstrated after the drug has been discontinued, one can then see why opioid agonist maintenance therapy becomes an effective approach to addressing heroin addiction. It should be emphasized, however, that maintenance therapy does not have to, nor should it, be used to the exclusion of other forms of support, including counseling, education, training and, perhaps most important, developing an understanding as to why drug use was initiated to begin with. All of these forms of support complement maintenance and should be pursued simultaneously.

In a review of the objectives of opioid agonist maintenance therapy (Table 3), the obvious immediately comes to mind. Drug craving should be eliminated, opioid withdrawal should not occur, and normal physiologic functions should be restored. However, unless continuing or recurrent heroin use can be prevented, maintenance therapy will be of little value. Prevention of heroin use is accomplished through maintaining a tolerance threshold sufficiently high to prevent euphoria from occurring, even if heroin is injected, through the mechanism of tolerance and cross-tolerance (14).

In identifying a specific agent for maintenance therapy of heroin addiction, certain charac-

TABLE 3
Objectives of Maintenance Therapy

Prevent opiate or other drug withdrawal (if a characteristic of a specific drug)
Prevent drug craving or drug hunger
Normalize physiologic function
Maintain at tolerance threshold to prevent euphoria
Prevent continued or recurrent use of illicit opiates or other targeted drugs of abuse
Allow psychologic and sociologic issues leading to drug use to be addressed by appropriate behavioral and other techniques
MAINTAIN ABSTINENCE, THAT IS, BE FREE OF ILLICIT USE OF DRUGS

teristics are essential (Table 4) (15). First, the medication must be effective after oral administration. Utilizing a parenteral agent carries with it the reinforcement of the conditioned responses related to intravenous self-administration that existed with heroin use. Second, the medication must have a long biological half-life so that an individual neither focuses on taking this substance more than once a day nor becomes excessively concerned when a dose is missed. Third, there must be minimal side effects associated with administration of the medication and no serious adverse effects. Fourth, the medication must be easy to use for a substantial percentage of persons addicted to heroin. Based on these objectives, therefore, the legalization of heroin or the establishment of heroin maintenance, irrespective of any moral issues, would be completely inappropriate (13, 15) (Table 5).

Methadone Maintenance

In reviewing these requirements, Dole et al. concluded in 1964 that the best and, at that time, only available synthetic opioid substance meeting such characteristics was methadone (Table 6) (14). Subsequently, a second agent, levo-alpha-acetylmethadol [LAAM], a congener of methadone which has an even longer half-life in humans (15, 16), was studied and approved, and utilized in treatment by the FDA. In fact, at that time, methadone was being used to treat chronic cancer pain. This is not surprising, since the same characteristics that made methadone attractive for maintenance therapy made it equally attractive for its use with chronic pain. Dole et al. demonstrated that methadone could be administered orally in a single daily dose, rather than 3–4 times a day. Subsequent studies showed that methadone has a duration of action in humans of 24–36 hours as contrasted with the 4-6 hours of heroin and morphine (14, 15). Furthermore, it was demonstrated that those patients who were placed on methadone with an initial dose of 20–40 mg/day and a stepwise dose increase of 5–10 mg every 4–7 days until a dose of 80–120 mg was reached, developed a tolerance threshold which other opioids could not overcome (14). The higher the dose of methadone, the greater the "blocking" effect of euphoria from heroin and other short-acting opioids. Furthermore, these investigators found that when a patient was being maintained on methadone, intravenous injection of comparable doses of methadone or of any other opioid tested were not associated with any narcotic effect, including respiratory depression or euphoria.

TABLE 4

Profile for a Potential Pharmacotherapeutic Agent for Treatment of Addiction

1. Effective after oral administration
    - – Minimal systemic bioavailability after oral administration > 35%
    - – Optimal systemic bioavailability after oral administration > 70%
2. Long biological half-life in humans
    - – Plasma apparent terminal half-life > 20–24 hours
    - – Specific receptor occupancy of > 20–24 hours
3. Minimal side effects during chronic administration
4. Safe, i.e., no true toxic or serious adverse effects
5. Efficacious for a substantial percentage of persons with the disorder (But does not need to be 90–100%; may be suitable for a small subset only — 15–20%)

TABLE 5

*Heroin Versus Methadone**

	Heroin	Methadone
Route of Administration	Intravenous	Oral
Onset of Action	Immediate	30 minutes
Duration of Action	3–6 hours**	24–36 hours
Euphoria	First 1–2 hours	None (if appropriate dose used)
Withdrawal Symptoms	After 3–4 hours	After 24 hours

* Effects of high dosages of drug or therapeutic agent in tolerant individuals.

** Includes action of major metabolite, morphine.

TABLE 6

Characteristics of Methadone in Maintenance Therapy

Highly Effective Orally
Bioavailability — 70–90%
Plasma levels in 30 minutes — peaks 2–4 hours
Steady state for 24 hours
Minimal withdrawal symptoms if dose is missed

Minimal Side Effects
Sweating — 50%
Constipation — 20%
No serious side effects at 25 years follow-up

Effectiveness
Successful in cessation of illicit opiate use — 60–90%

Dose dependent

Cost effective

The subsequent initiation of methadone maintenance for heroin dependency and its effectiveness in diminishing heroin use are well known by others (18). However, it is important to emphasize that studies have demonstrated that, with respect to the effects on the neuroendocrine system and immune function, maintenance therapy with methadone has been shown to reverse the abnormalities seen with heroin addiction, and does it without any toxic or serious side effects (15, 16). In reviewing the pharmacological actions of methadone, it is not surprising to find that this effectiveness has been demonstrated. When considering its pharmacokinetics, it would be surprising were this not the case. It is also important to emphasize that maintenance therapy with methadone will be effective only for opioid drugs, and will not have any effect in preventing withdrawal from or craving for any other group of mood-altering substances. It may also be belaboring the obvious to reiterate that methadone will be most effective in programs that combine maintenance with counseling, psychological support, education, and retraining.

Despite these observations and the elucidation of the principles of methadone maintenance during the previous three decades, the majority of health care providers have little or no understanding of either the concept of maintenance or the neurobiological actions of methadone. This lack of understanding is also prevalent in individuals running maintenance programs which have enrolled approximately 179,000 persons (19, 20). This lack of understanding also explains why the majority of patients on maintenance therapy are being treated with doses insufficient to raise their tolerance threshold high enough to prevent intravenous use of heroin. To reverse this situation, the neurobiology of opioid dependence and pharmacokinetics of these drugs must be appreciated if better approaches to the treatment of heroin addiction are to be achieved.

All clinical investigations described in this manuscript were conducted in accord with the guidelines of the Declaration of Helsinki and have been approved by the Institutional Review Board at The Rockefeller University Hospital.

Also, all experiments on animals reported in this manuscript were conducted in accord with the National Institutes of Health (US) guidelines for the care and use of laboratory animals and have been approved by the institutional office at The Rockefeller University which supervises such work.

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Cerebral Metabolism in Opiate-Dependent Subjects:

Effects of Methadone Maintenance

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Abstract

Background: The long-term effects of opiate use on human brain are not known. The goal of this preliminary study was to determine whether human subjects with histories of opiate dependence have persistent differences in brain function as compared with individuals without substance use disorders, and whether methadone maintenance reverses or ameliorates the potential abnormality.
Methods: Positron emission tomographic (PET) [18F]fluorodeoxyglucose (FDG) method was used to compare the regional cerebral metabolic rate for glucose (rCMRglc) in three groups: four opiate-dependent subjects currently receiving methadone maintenance therapy (MM), four opiate-dependent subjects not receiving methadone maintenance therapy (MW), and a comparison group of five subjects without substance use disorders.
Results: A significant difference in rCMRglc in the anterior cingulate gyrus was found between the MW and Control groups (Mann-Whitney $U = 2.0$, $p = 0.05$). Generally speaking, rCMRglc's in MM subjects were intermediate between those of MW and Control groups, although the difference did not reach statistical significance.
Conclusions: The results of this study suggest that neurobiological abnormalities can persist in the brain of a chronic opiate user several years after detoxification from methadone. Future research is needed to replicate these results and to determine whether the observed rCMRglc differences are related to opiate use or to neurochemical abnormalities that play a role in developing addictive behavior.
Key Words: Cerebral metabolism, opiate dependency, methadone maintenance.

Introduction

Opiate addiction has been a public health problem in the United States for more than 100 years. Since the availability of heroin has increased dramatically in the 1990s, the problem of opiate dependence has become more acute. It has been estimated that more than 2.7 million Americans have used heroin at some time in their lives, and that approximately one million meet the criteria for heroin dependence (1).

Methadone maintenance therapy (MMT) is the primary treatment offered to opiate-dependent patients in this country, and long-term treatment has been evaluated to be crucial for positive outcome (2, 3). Although marked by considerable controversy (patients remain physically dependent on medication, and many continue to use heroin and other illicit drugs), most treatment evaluation studies have shown that methadone maintenance therapy is effective. By binding to opiate receptors in the brain, methadone reduces drug-seeking behaviors, reduces or eliminates use of heroin, prevents opiate withdrawal symptoms, and stabilizes neuroendocrine functions (1, 4, 5). Methadone's long duration of action provides successful treatment with daily dosing, allowing patients to maintain relatively normal patterns of activity.

Methadone maintenance therapy reduces illicit opiate use, decreases the risk of HIV transmission, results in improved general health, and is associated with higher employment rates (3). It also reduces the antisocial behavior that accompanies the use of illicit drugs and the societal costs of opiate dependence (2, 3, 6–9). However, not

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Glossary: FDG [18F]fluorodeoxyglucose, a PET tracer; MM Receiving methadone maintenance; MW Not receiving methadone maintenance; PET Positron Emission Tomography; rCBF Regional cerebral blood flow; rCMRglc Regional cerebral metabolic rate for glucose; ROI Region of interest; SPECT Single Photon Emission Computed Tomography.

all patients respond to the same extent. Polysubstance users, patients with comorbid psychiatric histories, and patients receiving inadequate methadone doses have poorer prognoses than others (2, 3, 6, 10). Nonetheless, the net effect over time typically is the extinction of heroin use (11). Compared to newer medications such as buprenorphine, methadone maintenance therapy is of equal or greater effectiveness, as measured by retention in treatment, decrease in illicit opiate use, rate of abstinence and compliance with counseling (12–14)

The primary goal of this preliminary study was to determine whether human subjects with histories of opiate dependence have persistent differences in brain function as compared with individuals without substance use disorders, and whether methadone maintenance therapy reverses or ameliorates the potential abnormality. To this end, the positron emission tomographic (PET) [18F]fluorodeoxyglucose (FDG) method was used to compare the regional cerebral metabolic rate for glucose (rCMRglc) in three groups: opiate-dependent subjects currently receiving methadone maintenance therapy, opiate-dependent subjects not receiving methadone maintenance therapy, and a comparison group of subjects without substance use disorders.

There have been few brain imaging studies investigating the effects of opiates or opiate antagonist drugs on regional brain function (assessed by measuring regional cerebral blood flow or rCMRglc) in human subjects (15–18). In contrast, the effects of opiate administration on regional cerebral blood flow in subjects without histories of substance use were researched more thoroughly (19–26). These studies implicated the anterior cingulate gyrus as one of the key brain regions subserving pain and opiate-induced analgesia. The leading theories of opiate dependence invoke either the "Endogenous Opioid Deficiency Syndrome" (5) or an "Atypical Stress Responsivity" (27) to explain the disorder. They both posit the existence of excessive emotional pain in opiate users. It was, therefore, of interest to determine if the anterior cingulate gyrus would be among the brain regions to show a methadone-reversible abnormality in opiate-dependent subjects.

Methods

Subjects: Eight subjects diagnosed with opiate-dependence according to DSM-IV (four stabilized with methadone maintenance therapy [MM], four withdrawn from methadone [MW] and five control subjects participated in this preliminary study). All participants were right-handed. Subjects on MMT were recruited from the 23 methadone clinics operated by Beth Israel Medical Center and the 9 methadone clinics associated with Albert Einstein College of Medicine Hospitals and The Mount Sinai Hospital. For the MW group, subjects in full, sustained remission were recruited from former patients who had remained in contact with their methadone clinic counselors. Control subjects were recruited from support staff at Beth Israel Medical Center. They were somewhat younger than opiate-dependent subjects. The demographic characteristics of the subjects are presented in Table 1.

In order to establish psychiatric diagnoses, the Structured Clinical Interview for DSM-III-R (28) was administered along with the Mini-Mental Status Examination. Urine for toxicology was obtained three times: twice on the days of psychometric testing and once before the PET scan. HIV tests, CBC, and SMA-7 were also obtained from the subjects prior to the PET scan. The subjects were paid for participation in the study.

Subjects were both male and female; they were included in the study if they were between 21 and 45 years of age, and were able to demonstrate an understanding of the study before giving written consent. A DSM-IV diagnosis of opiate dependence in the past 2 years, established by structured clinical interview for diagnosis (SCID), was an inclusion criterion (28). The MM subjects were required to be on a stable dose of methadone for at least 6 months prior to entering the study. A requirement for the MW was a period of at least 6 months since detoxification from methadone maintenance therapy. Subjects were

TABLE 1

Characteristics of Subjects

	Controls	Opiate-dependent Subjects	
		MM	MW
N	5	4	4
Gender (male/female)	3/2	2/2	2/2
Age (yrs)	25.6 ± 1.7	38.0 ± 5.8	38.0 ± 1.4
Education (yrs)	15.0 ± 2.0	11.5 ± 4.7	14.0 ± 3.2
Years of opiate abuse	—	13.6 ± 10.1	7.8 ± 1.7
Years of MMTP	—	4.3 ± 3.4	9 ± 9.4
Years on stable dose of methadone	—	1.5 ± 1.4	—
Years since detoxification	—	—	4.3 ± 1.7

MM = methadone maintenance therapy group
MW = group not receiving maintenance

excluded if they had: a current or lifetime history of any Axis I diagnosis other than opiate dependence and nicotine dependence; a history of cocaine use within the 6 months prior to the study; central nervous system (CNS) disease; cardiovascular, pulmonary or systemic disease; or HIV-seropositivity. Moderate alcohol or caffeine use was not an exclusion criterion.

PET Scanning

Scanning procedure. Brain imaging was performed using a Posicam 6.5 PET scanner (Positron Corp., Houston, TX), and FDG was purchased from the CTI Services, Inc. PET Distribution Center (New York, NY). The Posicam 6.5 is a 21-slice instrument with a 5.125-mm inter-slice distance. The spatial resolution of the tomograph is 5.8 mm in-plane and 11.9 mm in the z-axis. The sensitivity of the camera, measured with a 20-cm diameter cylindrical phantom (system sensitivity), is (165 counts/μCi/cm^3/axial cm).

Prior to injection of the radiotracer, the subject was positioned in the scanner gantry and his/her head was immobilized with a thermoplastic mask. A 20-min transmission scan, using a Ga/Ge rod, was performed to measure the attenuation of photons by the brain and skull. For the FDG injection, a catheter was placed into a left forearm vein. The subjects received one injection of FDG (5 mCi, 185 mSv), and an emission scan (approximately 20 min) was initiated approximately 30 min after the FDG injection. Following the scan, the subject was removed from the tomograph and instructed to void, to reduce the radiation dose to the bladder (29). From the time of the FDG injection until the end of the scan, lighting in the room was dimmed, and the subject was instructed to stay awake but keep his/her eyes closed.

Image Reconstruction. Images were corrected for attenuation and reconstructed utilizing a spatially-varying convolution-scatter subtraction technique and a Butterworth filter. Raw counts were used for PET scan analysis, and the data were transferred to a SUN workstation for image analysis. The global raw counts were measured on all images that contained the brain. The threshold-based region growing algorithm in ANALYZE (Digital Equipment Corp., Houston, TX) was used to outline the brain on all slices in which it appeared. The global raw count was taken as the mean of the mean raw counts for each slice. The raw count image was normalized by dividing the raw count of the specific region of interest by the global raw count of the subject.

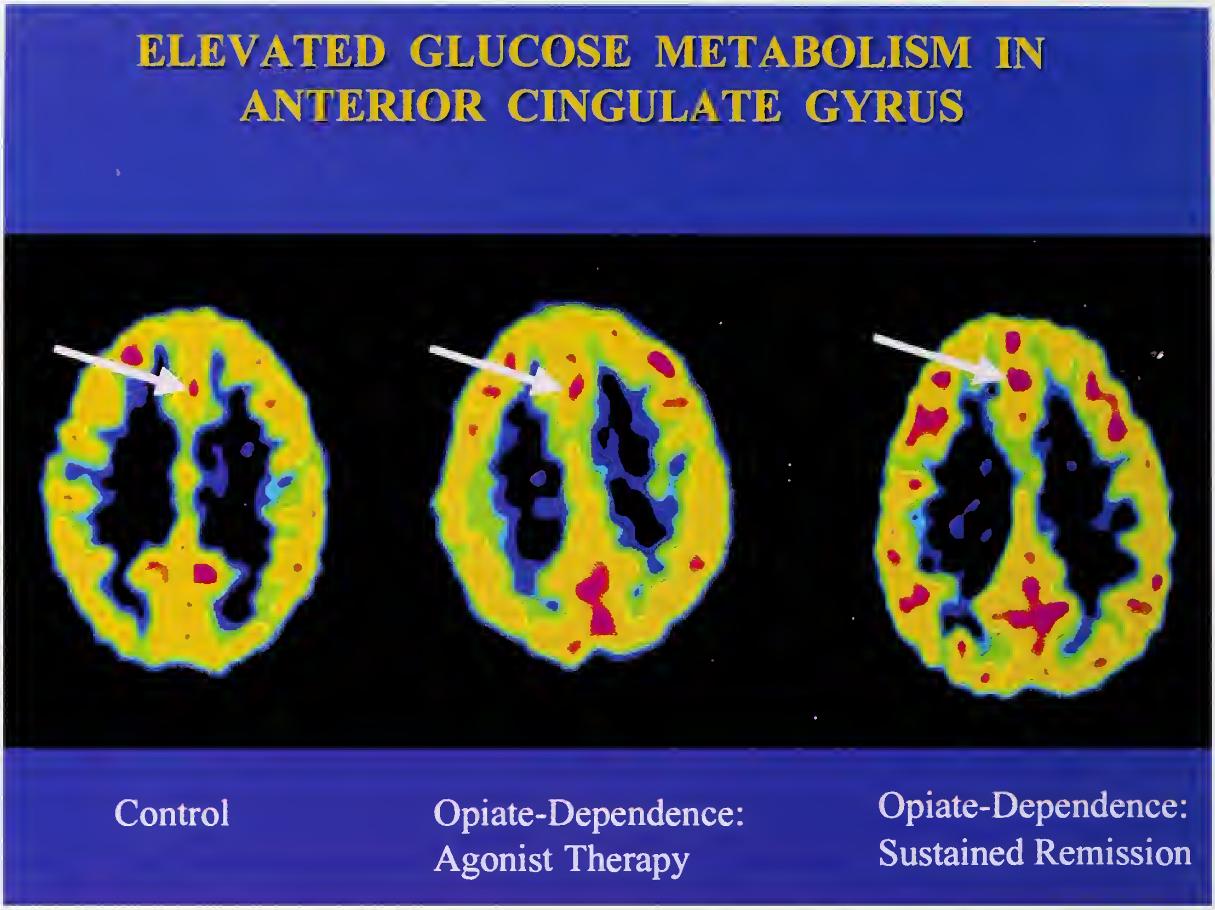
Image Analysis. Image analysis was performed by an investigator blind to the identity and diagnosis of each subject. Using a standard template, 38 bilateral regions of interest (ROIs) were placed on PET images and individually adjusted to account for differences in neuroanatomy. The ROIs were: template 1 (left and right temporal pole, left and right cerebellar hemisphere); template 2 (left and right medial orbitofrontal cortices, left and right lateral orbitofrontal cortices, left and right superior temporal cortices, left and right middle temporal cortices, and left and right hippocampi); template 3 (left and right caudate heads, left and right putamens, and left and right thalami); template 4 (left and right ventral superior frontal cortices, left and right ventral middle frontal cortices, and left and right middle occipital cortices); template 5 (left and right anterior cingulate gyri, left and right dorsal superior frontal cortices, left and right lateral dorsal frontal cortices, and left and right angular gyri); and template 6 (left lateral parietal cortex, and left and right dorsal parietal cortices).

Statistical Analysis. In a preliminary screening procedure, potential group differences in rCMRglc were evaluated by separate Kruskal-Wallis ANOVA's, performed on values from each ROI. In order to avoid false positive findings, only the relative magnitudes of the Mann-Whitney U test statistics were examined, and the ROI yielding the lowest value was selected for modeling via Generalized Estimating Equations (30, 31). In the primary analysis, rCMRglc values taken from right- and left-hemispheres in each subject were treated as repeated measures. The model treats rCMRglc as a continuous variable with an approximately Gaussian distribution.

Results

Even unprotected by correction for multiple comparisons, the preliminary data screening procedure yielded only one Mann-Whitney U statistic significant at $p < 0.05$. The significant difference was between the MW and control groups in the anterior cingulate gyrus (Mann-Whitney $U = 2.0$, $p = 0.05$) (Fig. 1). Group descriptive statistics for left and right hemisphere rCMRglc values for the anterior cingulate gyrus are given in Table 2. Accordingly, rCMRglc in anterior cingulate gyrus was regressed on hemisphere (L, R) and group membership (MM, MW, dummy coded with controls as reference) in a Generalized Estimating Equations model:

$$\text{rCMRglc} = \text{Intercept} + \beta_1(\text{Hemisphere}) + \beta_2(\text{Group 1}) + \beta_3(\text{Group 2}).$$



ELEVATED GLUCOSE METABOLISM IN ANTERIOR CINGULATE GYRUS

Control

Opiate-Dependence: Agonist Therapy

Opiate-Dependence: Sustained Remission

Figure. Brain metabolic images at the level of corpus callosum for methadone-maintained and methadone-withdrawn subjects with histories of opiate dependence and control subjects. Arrows point to the anterior cingulate gyrus where ROIs were placed and activity measured.

TABLE 2

Regional Cerebral Metabolic Rate for Glucose of the Anterior Cingulate Gyrus

	Intercept	Hemisphere	Group 1	Group 2
β	1.3614	0.0303	0.1147	0.1025
S.E.	0.0377	0.0413	0.0299	0.0350

Group 1 = methadone maintenance group
Group 2 = methadone withdrawal group

Overall, the analysis resulted in a Wald χ^2 value = 15.41, (df = 3), $p < 0.01$, with parameter estimates and their standard errors as follows: Here, the β coefficients were effect sizes, scaled to the metric of the dependent measure. Hence, holding hemisphere constant, MM subjects had values of rCMRglc that were 0.1147 μCi/mL greater than those of controls and rCMRglc's in MW subjects was 0.1025 μCi/mL greater. The model also yielded standardized parameters (Estimate/S.E.) that served as significance tests of the β_i's. The test for hemisphere was not significant (z_H = 0.74), but those contrasting the MM and MW groups with controls were significant (z_{MM} = 3.84, $p < 0.001$ and z_{MW} = 2.93, $p < 0.01$). Holding the control group membership constant, further exploration of the contrast between the MM and MW groups was afforded by a Wald test statistic for H_0: $\beta_1 = \beta_2$, which yielded no significant difference (z = 0.42). Generally speaking, however, rCMRglc's in MM subjects were intermediate between those of MW and control groups.

These results indicated significantly higher rCMRglc's in both MM and MW subjects compared to that of control subjects. However, in view of the age difference between opiate-dependent subjects and controls, age might have been a confounding factor in this result. In order to address this concern, a *post hoc* analysis was conducted in which each subject's age was added as a covariate to the model tested above; its associated β coefficient is -0.0020 ($z = 0.70$, $p = ns$) and it appeared not to figure importantly in this model.

Discussion

The results of this study suggest that neurobiological abnormalities can persist in the brain of a chronic opiate user several years after detoxification from methadone. At present, there are no data in the literature for direct comparison with the results of this study and there are only a handful of PET and single photon emission computed tomography (SPECT) studies on the effects of acute opiate administration, opiate withdrawal, and chronic opiate use on rCMRglc and regional cerebral blood flow (rCBF). Some of the studies showed changes in the anterior cingulate gyrus; most were performed on polysubstance users.

London et al. (15) used FDG PET methodology to demonstrate that in polydrug abusers, morphine, primarily a mu-opioid agonist, reduced rCMRglc in a number of telencephalic and subcortical structures, with a significant global effect. As buprenorphine, a mixed opioid agonist/antagonist, had similar effects (16), it was suggested that the primary effect on rCMRglc was through an action as a mu-opioid agonist.

Only two preliminary ^{99m}Tc HMPAO (Ceretac, Amesham, Ltd., U.K.) SPECT studies of rCBF during "opiate withdrawal" have been published (17, 18). Krystal et al. (18) reported that in subjects receiving methadone maintenance treatment, symptoms of withdrawal after acute naloxone administration were associated with lower global perfusion, lower activity ratios in the frontal and parietal cortices, and increased thalamic activity. Van Dyck et al. (17) studied the effects of naltrexone-precipitated opiate withdrawal in active heroin users after a 7-day buprenorphine treatment. Compared to placebo, naltrexone-precipitated withdrawal resulted in no significant changes in rCBF ratios, but the severity of opiate withdrawal was negatively correlated with rCBF in the anterior cingulate gyrus. The authors related their finding to a role of anterior cingulate gyrus in processing the emotional, suffering component of pain (21, 32).

The PET and SPECT studies of "chronic opiate" use did not show rCBF and rCMRglc changes in the anterior cingulate gyrus. Krystal et al. (18) studied the effects of chronic opiate use on rCBF using ^{99m}Tc HMPAO SPECT in a group of polysubstance users on methadone maintenance treatment. The extent of illicit drug use in this group is unclear, although with one exception, all subjects were free of drugs, as judged by weekly urine toxicologies and clinical records. The authors reported that subjects on methadone maintenance treatment had lower perfusion rates in the frontal and parietal cortices and greater perfusion rates in the thalamus, compared to healthy controls. In a study of cocaine-using polysubstance users, Holman et al. (33) found a higher number of focal perfusion defects in the temporal, inferior parietal, and anterior frontal cortices of those patients, compared to healthy subjects. A more extended pattern of metabolic abnormalities in polydrug cocaine/opiate abusers involving decreased absolute rCMRglc in the lateral occipital gyrus, temporal, and orbitofrontal cortices was detected in FDG PET studies by Stapleton et al. (34).

In addition to brain studies investigating neurobiological effects of opiates in opiate-dependent subjects, the anterior cingulate gyrus was implicated in PET studies as being one of the key brain regions subserving "analgesia and pain" in subjects without histories of opiate use. Morphine "analgesia" decreased the affective-motivational, but not the sensory dimension of pain in a case report of a patient suffering from cancer (32). In this preliminary study, rCBF measured with PET using $C^{15}O_2$ revealed that morphine analgesia was associated with an increased perfusion in the temporal, prefrontal and the anterior cingulate gyri (32). Another PET study, this one measuring rCBF in opiate-naive, healthy volunteers showed that fentanyl analgesia increased rCBF in the anterior cingulate gyrus, and motor and prefrontal cortices, and decreased rCBF in the thalamus and posterior cingulate cortex (20). This activation pattern was also associated with decreased pain perception. Both studies demonstrated a similar pattern of activation, including the anterior cingulate gyrus and related prefrontal cortex during opiate administration and analgesia.

A number of rCBF PET studies using ^{15}O-labeled tracers indicate that in healthy subjects, "pain" increases regional cerebral blood flow in the anterior cingulate gyrus, especially Brodmann area 24 (20–26). Pain also resulted in increased activity in the lentiform nucleus, periaqueductal gray, and prefrontal cortex (22, 24, 35); thalamus and supplementary motor area (20, 24); and insula and somatosensory cortex (21, 22, 24). These structures are either a part of or are closely related to the "medial pain system" (36). The anterior cingulate gyrus represents the brain region most consistently activated by pain stimuli.

In view of the above, there are two possible interpretations for our findings: (1) Chronic use of illicit opiates or MM is associated with elevations in the rCMRglc in the anterior cingulate gyrus, which persist after cessation of opiate use, and are long lasting (over several years). From our study design it is impossible to determine whether the observed rCMRglc differences are related to illicit opiate use or result from opiate maintenance. (2) The observed rCMRglc elevations in the MM and MW subjects (compared to controls) preceded opiate use and could be related to neurochemical abnormality that plays a role in developing addictive behavior.

The neurobiological basis for the observed rCMRglc differences in the anterior cingulate gyrus is unclear at this time. Based on early neurosurgical studies as well as on functional brain imaging work detailed above, Vogt et al. (26) proposed that activation of the anterior cingulate gyrus during the pain PET paradigms was associated with the affective-motivational, suffering component of pain. Similar increase in rCBF of the anterior cingulate gyrus was observed during morphine-induced analgesia and associated euphoria (37), suggesting powerful regulation of the anterior cingulate gyrus by opiate compounds (26) and a close relationship between opiates and affect and mood. The relationship between opiate-related elevations in the rCBF in the ventral anterior cingulate gyrus and affect are further supported by reports of similar rCBF elevations during PET studies of sadness in healthy women (38). Therefore, the observed differences in the anterior cingulate gyrus in patients with histories of opiate dependence compared to control subjects are not inconsistent with the existence of excessive emotional pain in opiate abusers posited by "Endogenous Opioid Deficiency" (5) and "Atypical Stress Responsivity" (27) theories of opiate dependence.

The results of this study should be considered within its limitations, which include small sample size, poor demographic matching of the control group to patient groups, and limited spatial resolution of the Posicam PET. Nonetheless, the results of this study suggest that specific neurobiological abnormalities, i.e., elevated rCMRglc in the anterior cingulate gyrus, may persist in brains of chronic opiate users several years after methadone detoxification. Further research is needed in order to validate these preliminary findings and to explore whether the rCMRglc differences in the anterior cingulate gyrus observed in this study result from or precede opiate dependence.

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Methadone Medical Maintenance (MMM):

Treating Chronic Opioid Dependence in Private Medical Practice — A Summary Report (1983–1998)

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Abstract

Methadone Medical Maintenance (MMM) was implemented in 1983 to enable socially rehabilitated methadone patients to be treated in the offices of private physicians rather than in the traditional clinic system. Over a period of 15 years, 158 methadone patients who fulfilled specific criteria within the clinic system entered this program in New York City. Participating patients reported to their physician once a month and received a one-month supply of methadone tablets rather than a one-day liquid dose in a bottle.

Of the 158 patients who entered this program, 132 (83.5%) were compliant with the regulations and proved to be treatable within the hospital-based private practices of internists participating in the program. Compliant MMM patients found it easier to improve their employment status and business situations, finish their educations, and normalize their lives in MMM as opposed to the traditional clinic system because they had simplified reporting schedules and fewer clinical restrictions. Twelve (8%) compliant patients were able to successfully withdraw from methadone after an average of 17.7 years of treatment in both the traditional clinics and MMM. Twenty compliant patients (13%) died from a variety of causes, 40% of which were related to cigarette smoking. None of the deaths were attributable to long-term methadone treatment. Other causes of death included hepatitis C, AIDS, cancer, homicide, complications of morbid obesity and meningitis.

The 26 noncompliant patients (16.5%) were referred back to their clinics for continued treatment or were discharged for failure to report as directed. A major cause of failure in MMM was abuse of crack/cocaine.

Stigma concerning enrollment in methadone treatment was a major social issue that patients faced. Many refused to inform employers, members of their families, friends, and other physicians who treated them for a various of conditions that they were methadone patients. The methadone medical maintenance physician, therefore, functions as a medical ombudsman for the patient, educating other physicians who treat the patient about methadone maintenance and its applicability to the patient. Our results can serve as a model for the expansion of office-based MMM treatment.

Key Words: Heroin addiction, methadone, methadone maintenance, methadone medical maintenance, private practice.

Introduction

Methadone maintenance treatment (MMT) for heroin addiction was first developed at The Rockefeller University as an outpatient clinical program from 1964 to 1970 (1, 2). From the inception of its use in maintenance treatment, methadone has been shown to be effective and medically safe (3, 4). Over the past 35 years, methadone maintenance has been implemented in outpatient clinics throughout most of the United States. Approximately 179,000 patients were in treatment in 1998, about 44,000 of them in New York State (5). Evaluations of methadone maintenance treatment (MMT) over the past 30 years and reviews by the National Institutes of Health and the Institute of Medicine have shown methadone maintenance to be the most effective treatment for heroin addiction (6–9).

Traditional methadone clinics serve an important purpose for methadone patients with social and medical problems, especially when they begin MMT. However, the counseling services available in clinics for patients with serious problems (e.g., abuse of drugs and alcohol, chronic unemployment, homelessness, behavioral problems, emotional instability, etc.) are seldom needed by socially rehabilitated patients (6, 7). Furthermore, the clinics are highly regulated, with specific rules about reporting (6, 7). While useful for patients who need services and structure, they are constricting and counterproductive for socially rehabilitated patients who have stopped using illegal drugs, have obtained steady employment, and fulfill family responsibilities (6, 7).

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For example, approval from various levels of government must be obtained for exemptions to regular policy on issues such as extended travel for business and vacations. Also, patients must stand on lines while waiting to be serviced. The locations of traditional clinics can compromise the confidentiality of patients who may report to neighborhood clinics. They can be identified as patients not only by other patients, but also by neighborhood residents who can observe the patient enter and leave the facility. In traditional methadone maintenance clinics, the medication is dispensed in bottles containing the patient's daily dose in liquid form. This may cause problems with storage or concealment if the patient receives several bottles to take home or goes on a business trip or vacation.

Supported by the New York State agency now known as the Office of Alcoholism and Substance Abuse Services (OASAS), methadone medical maintenance (MMM) was started in 1983 at The Rockefeller University by Dr. Marie E. Nyswander. Its purpose was to treat rehabilitated methadone maintenance patients who wanted to continue methadone maintenance treatment but did not need the services and structure of traditional methadone clinics (10–12). In MMM, methadone is prescribed and dispensed to patients at least one or more times a month by physicians in the privacy of their offices, in contrast to patients reporting to traditional clinics daily, one or more times a week. Therefore, methadone treatment and methadone patients are better integrated into mainstream medical practice than they would be in the isolated clinics (10–12).

In 1985, the program was transferred to physicians affiliated with the Division of Chemical Dependency in the Department of Medicine of the Beth Israel Medical Center and the Family Care Group Practice at St. Luke's Hospital in New York City. Subsequently, with the closing of the St. Luke's Program in 1993, all patients were transferred to the Beth Israel Program. Physicians recruited to treat patients in this program were internists with hospital-based and family care practices at the Beth Israel Medical Center. Only one of these physicians had clinical experience treating methadone patients. These newly recruited doctors integrated the patients into their practices after receiving training supervised by physicians with experience treating methadone patients.

In MMM, patients receive their monthly medication in the form of dry "diskettes" in one or two bottles depending on the dosage prescribed. Dispensing of methadone in diskette form facilitates storage of the medication and its concealment from family members or friends, who may not know the patient is enrolled in the program. The patients allocate the proper daily amount, dilute the diskettes in water or juice, and drink the medication in the privacy of either the physician's office or their homes, as opposed to taking it in a clinic.

From its inception, MMM operated under a series of IND (Investigational New Drug) permits issued by the Food and Drug Administration (FDA). The program also is approved by the Drug Enforcement Agency (DEA) and the Institutional Review Board of the Beth Israel Medical Center. The New York State OASAS has supported and encouraged the development of this model of MMM.

This article summarizes the MMM program as currently operated at Beth Israel Medical Center in New York City from its inception in June of 1983 at The Rockefeller University through August of 1998, a period of more than 15 years. The criteria for admission, a description of the patient population, retention statistics, the role of the physician, medical problems, reasons for termination, causes of death, stigma issues, and examples of improvements in the patients' personal and social functioning will be reviewed.

Criteria for Admission

The following criteria were established to select patients who still needed the services provided in the clinics, but who established a pattern of stability, could be treated by a private physician, and could benefit from the program:

- a minimum of 5 years in methadone treatment; this was modified in 1996 to 4 years. However, no patients who applied had less than 6 years of treatment in conventional methadone programs

- for at least three years prior to entry

  — no illicit drug use, excessive alcohol use, or criminal activity

  — stable employment or verified reliable income and/or productive activity such as homemaking, or enrollment in school or college

  — compliance with clinic regulations, submitting of urine tests, reporting as directed to the clinic, responsibility in handling of medication (e.g., no losses or evidence of diversion)

- emotional stability, as assessed from clinic records and personal interviews
- a verifiable means of financial support to meet payments
- no social ties to illicit drug users or street activities that can precipitate relapse
- a statement from the clinic staff that patient can benefit from methadone medical maintenance and meets the criteria for admission to the program
- patient and referring clinic agree that methadone medical maintenance is important to facilitate improvements in the patient's quality of life
- if patient is under care for a serious chronic medical condition or emotional disorder and is prescribed medication, the patient must allow the medical maintenance physician to contact the other health care providers to exchange relevant medical information
- the patient enters the program voluntarily
- the patient is not in the armed forces
- the patient can safely store a month's supply of medication

Recruitment of Patients and Procedures of the Program

Patients are recruited from methadone maintenance programs in the Greater New York City area. Letters are sent to the clinic directors notifying them about the program and the criteria for admission. The clinics then submit records of candidates for MMM to the medical director of the MMM program and to the Bureau of Methadone Planning and Policy of the New York State Office of Alcoholism and Substance Abuse Services, for further evaluation. After the records are approved, the patients are interviewed by the medical director of the MMM program. If appropriate and if the patient agrees, he or she is transferred to the methadone medical maintenance program. The transfer is entered into the New York State Methadone registry operated by Creative Socio-Medics. Alternatively, patients may contact the Medical Director of MMM directly. Patients who initiate their referrals must then go through the same process as other applicants.

Initially, patients report every two weeks for one month to a physician approved by the program and then are placed on monthly reporting schedules. At each office visit, patients submit a urine sample for analysis to determine whether they are refraining from use of illegal drugs and whether they are taking their prescribed methadone. Patients also drink a dose of methadone at the visit, to demonstrate that tolerance to the prescribed dose is maintained. Employment is verified through salary receipts and income tax statements. As in the clinic programs, patients receive annual physical examinations. The physician discusses social and/or personal problems that patients may have encountered and, if indicated, may refer patients for further counseling or assistance. The physician also discusses medical problems that patients present and can either assume responsibility for primary care or refer patients to other physicians. The patient pays a predetermined fee either through personal check or insurance coverage.

At the time of their office visits, the patients receive up to a monthly supply of methadone diskettes. The diskettes are ordered by the physician from the hospital pharmacy. They are stored in a safe in the physician's office the day before the patients' appointments.

Patient demographics for the group in this study, as well as their addiction and criminal histories are summarized in Table 1. Continuous variables are expressed as mean with standard deviation. Variables associated with demographics, addiction and criminal histories of patients who were in good standing — those who remained active, received a favorable termination from treatment, or died but were compliant patients when alive — were compared to the variables of patients who received unfavorable terminations. The standard t test and the chi square were employed to determine statistical significance inferred at $p < 0.05$. Life table analysis using SPSS (Statistical Package for the Social Sciences) was applied to investigate retention of 158 patients for a period of up to fifteen years.

Descriptive Data, Cumulative Retention and Reasons for Discharge

Table 1 summarizes demographic information and the addiction, criminal, and methadone maintenance treatment histories of the 158 patients at the time of their admissions to MMM distributed

TABLE I

Data for 158 Patients at Time of Admission to the MMM Program

1A — Demographic Data	Compliant n = 132 %	Noncompliant n = 26 %
Gender		
Female	27	23
Male	73	77
Ethnicity		
African American	7	0
Hispanic	12	12
Non-Hispanic (White)	81	88
Married*	68	46
Education		
Less than HS	12	19
HS graduate	63	58
College graduate	24	24
Employment		
Full time job	92	91
Part time/benefit	8	9
1B — Addiction History	**Years**	**Years**
Age @ heroin first use	18.5 ± 4.5	17.5 ± 4.2
Age @ first use of needles	19.5 ± 4.2	18.3 ± 4.2
Duration of heroin use	9 ± 11	13 ± 17
1C — Criminal History		
% with known arrests	70	66
Age (years) @ first arrest	20 ± 5	19 ± 5
Number of arrests	6 ± 12	5 ± 6
Months incarcerated	13 ± 27	16 ± 29
1D — Methadone Treatment History		
Age first admitted to Methadone Maintenance Treatment	27.6 ± 6.9	27.6 ± 6.2
Years in Methadone Maintenance Treatment**	16 ± 5	13 ± 5
% patients with one admission	64	89
% patients with two or more admissions***	36	12
Age admitted to MMM	43.8 ± 8.7	40.5 ± 7.7
Dose at admission mg/d to MMM	56.9 ± 31.6	59.6 ± 23.7

HS=High School
mean ± standard deviation
The difference between compliant and noncompliant patients is not significant except for: * $p < 0.03$, ** $p < 0.002$, and *** $p < 0.02$.

according to future compliance or noncompliance with the regulations of the program. The patients in MMM are socially rehabilitated, on the average older than patients who enter the clinic system (13) and economically within the working, middle, and upper-middle classes, with intact families. Of the 158 patients who entered the program, 132 (83.5%) were compliant with the regulations of the program and proved to be treatable within the private-hospital-based medical practices of the internists who were affiliated with the program. The remaining 26 patients (16.5%) were noncompliant and terminated from the methadone medical maintenance.

Statistically significant differences between compliant and noncompliant patients were noted in marital status, number of episodes of methadone maintenance treatment, and the duration of methadone treatment prior to admission to the methadone medical maintenance program. A higher proportion of compliant patients were either married or lived in stable relationships at the time of their admissions, as compared to the noncompliant patients (68% vs. 46%, $p < 0.03$). This suggests that as a group the patients with stable relationships are more likely to comply with the regulations of the program. Also, a higher proportion of compliant patients had two or more admissions to conventional methadone treatment prior to entering the MMM program than did the noncompliant patients (36% vs. 12%, $p < 0.002$). This may imply that compliant patients had committed themselves to long-term methadone maintenance treatment because they were unable to abstain from illicit use of heroin following withdrawal from methadone after previous episodes of treatment. Noncompliant patients had significantly shorter durations of treatment in the traditional methadone clinics prior to entering MMM than did compliant patients (12.5 years vs. 15.8 years, $p < 0.02$). Compliant patients, therefore, had additional time in the traditional clinics to resolve problems that could jeopardize a stable adjustment in MMM.

The figure shows the cumulative retention in MMM of the 158 patients over a period of fifteen years. All of the 158 had sufficient time in treatment for us to calculate the cumulative proportion of those remaining in treatment at the end of one, two and three years (98.7%, 95.6% and 88.6%, respectively). The cumulative proportion of patients enrolled in the program at five (n = 94), ten (n = 48), and fifteen years (n = 10) is 72.4%, 58.8%, and 44.6%, respectively. The declining number of patients over time reflects patients who were discharged and active patients who had short periods of treatment and therefore did not meet the retention criteria for particular intervals of time during the 15-year period of observation. The projected median retention time in MMM for this group of patients is 13.8 years. Sixty-five percent of the group of patients whose participa-

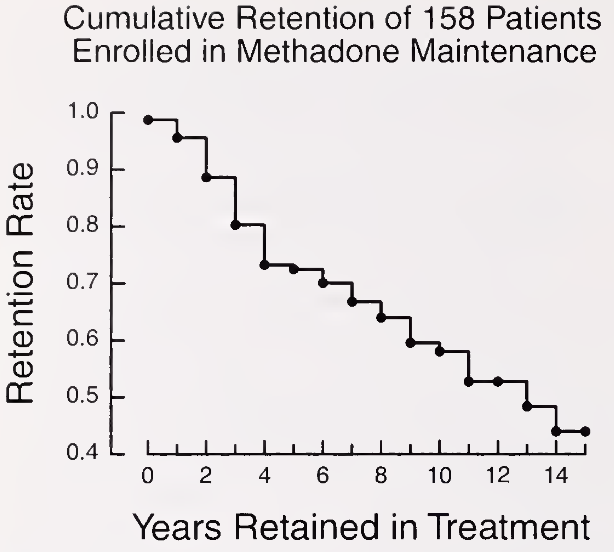

Figure. Cumulative retention of 158 patients enrolled in Methadone Medical Maintenance.

tion was terminated were discharged from MMM in their second through fifth years of treatment.

Tables 2A, 2B, and 2C summarize the outcome status for the 158 patients who were treated for up to fifteen years. Of the 132 patients (83.5%) considered compliant, 99 (62.7%) were alive and active in treatment, reporting once per month for their medication, maintaining their social stability through employment, education, retirement activities, family life, and abstaining from use of illegal drugs. Of the thirteen patients (8.2%) who left alive in good standing, twelve successfully withdrew from methadone. One patient in good standing returned voluntarily to the methadone clinic. This patient worked in the same building in which methadone medical maintenance was administered and was concerned about the possible loss of employment if enrollment in methadone treatment was discovered.

TABLE 2

Status of 158 Patients as of August 1998
Outcomes of Patients in MMM over a 15-Year Period

2A — Outcome	Number of Patients (%)
Compliant Patients	132 (83.5)
Active in good standing	99 (62.7)
Favorable withdrawal from methadone	12 (8.2)
Voluntary transfer back to methadone clinic	1 (0.6)
Deaths	20 (12.7)
Noncompliant Patients	26 (16.5)

2B — Causes of Deaths	Number of Patients (%)
Smoking related	8 (40)
Lung cancer	4 (20)
Heart disease	3 (15)
Emphysema	1 (5)
Hepatitis C	4 (20)
AIDS	3 (15)
Cancer (lymphoma)	1 (5)
Brain aneurysm	1 (5)
Meningitis	1 (5)
Complications of morbid obesity	1 (5)
Homicide	1 (5)

2C — Reasons for Discharge of 26 Noncompliant Patients	Number of Patients (%)
Serious cocaine problems	15 (58.0)
Administrative	7 (27.0)
Misuse of medication	4 (15.0)

The twelve compliant patients who successfully withdrew from methadone had on the average shorter histories of methadone maintenance treatment in conventional clinics prior to their entry into MMM than the other 120 compliant patients (12.9 ± 3.7 years vs. 16.1 ± 4.9 years, $p < 0.002$). They remained in MMM for 4.8 ± 2.3 years. The average total years of methadone treatment — the conventional clinic plus MMM — for the patients who successfully withdrew from methadone was 17.7 ± 4.8 years. Eight of the twelve were located and interviewed by phone. They reported that they were abstinent from use of narcotics for periods ranging from one to eight years. One of the former patients reported periods of drug hunger, relapsed to heroin use after five years of abstinence and applied for readmission to methadone maintenance treatment. Another patient in psychotherapy was receiving medication for depression.

Although not statistically significant, a clinical trend that has to be further investigated is that the compliant patients who were able to successfully withdraw from heroin had on the average shorter histories of heroin addiction than other compliant patients (5.8 ± 3.6 years vs. 9.3 ± 10.3 years). This trend coincides with reports in the literature that a duration of heroin addiction of about five years or less, a long duration of methadone maintenance of five or more years, and social stability at time of discharge are associated with successful abstinence after withdrawal (14, 15). However, biological factors may also be a factor in sustained abstinence. (16, 17).

Twenty compliant patients (13%) died from various causes, none of which were attributed to long-term methadone treatment. Eight patients with histories of smoking died from lung cancer (4), heart disease (3), or emphysema (1). Tobacco-related illnesses comprise 40% of the deaths in MMM.

Four patients died from complications related to hepatitis C, and three patients died from complications related to AIDS. Therefore, the number of deaths from smoking-related diseases was greater than the deaths from both AIDS and hepatitis C. The remaining five deaths were caused by cancer (lymphoma), a brain aneurysm, meningitis, complications of morbid obesity and a homicide (street violence). The crude death rate for MMM as of August, 1998 was 17 deaths per 1,000 patient years. The mean age at time of death was 57.7 ± 10.3 years, age range from 37 to 74 years. Patients who died had on the average 79 ± 49 months of treatment in methadone medical maintenance.

Twenty-six patients (16.5%) left MMM for noncompliance after 4 ± 2.67 years in MMM: eleven (6%) did not adhere to regulations of the program by either misusing or losing their medication, failure to report as directed, not meeting their payments, unacceptable behavior in a physician's office, and two were arrested for fraud and possession of cocaine; fifteen patients (10%) were terminated for serious abuse of cocaine/crack that could not be treated within private practice. Eighteen patients (11%) who left treatment for noncompliance were returned to their clinics of origin, two (1%) were incarcerated and the whereabouts of five noncompliant patients (3%) are unknown.

The majority (58%) of the 26 discharges were involved with cocaine and/or cocaine/crack. Except for two patients who entered treatment in the 1990s, these noncompliant patients were in the first cohort of 100 patients who entered the program during the 1980s at the peak of the cocaine/crack epidemic which began in the early 1980s. Fifty-five patients who entered MMM in the late 1980s and 1990s after the initial years of crack epidemic did not abuse this drug.

Table 3 shows the range of doses for 99 active patients by area of employment as of August 1998. The doses are considered appropriate by both the patients and the physicians, with 42% of the patients in the range of 80 to 120 mg/d. The range of doses in the program demonstrates that doses must be individualized to permit patients to function optimally and to eliminate the use of heroin. There is no correlation between employment and dose, since at every dose level patients are employed in a variety of jobs that demand similar physical and mental skills. For example, of the 9 patients who are CEOs or owners of businesses, 6 are receiving doses in the range of 80 to 120 mg/d and 3 are receiving doses in the range of 5 to 70 mg/d.

TABLE 3

Dose, by Number of Active Patients, by Area of Employment

n = 99

Dose Mg/d	Number of Patients	Area of Employment
5–25	10	1 business owner, 3 skilled laborers, 2 drug treatment counselors, 1 waiter, 1 office manager, 1 draftsman, 1 retiree
30–40	23	1 commercial artist, 2 skilled laborers, 2 drug treatment counselors, 1 construction worker, 4 salespeople, 1 teacher, 2 computer technicians, 5 administrators, 1 secretary, 1 health services, 2 drug counselors, 1 retiree
50–70	24	2 business owners, 1 laborer, 3 drug treatment counselors , 1 musician, 2 computer technicians, 3 administrators, 4 salespeople, 3 electronic repair workers, 1 paralegal, 1 electrician, 3 retirees
80	17	4 business owners, 1 skilled laborer, 1 porter, 1 administrator, 2 office services, 1 baker, 1 landscaper, 1 computer technician, 1 pattern maker, 1 drug treatment counselor, 1 bookkeeper, 1 customs officer, 1 homemaker
90–120	25	2 business owners, 3 administrators, 1 musician, 1 fireman, 1 court stenographer, 1 drug treatment counselor, 3 salespeople, 1 health professional, 1 administrative assistant, 1 computer technician, 2 maintenance service workers, 1 paralegal, 1 psychologist (Ph.D.), 1 electrician, 1 attorney, 1 video producer, 3 retirees

Discussion

Advantages for Patients

The patients in MMM have reported many advantages of being treated by a private physician over the clinic situation, including improved medical care, more secure confidentiality, greater self-confidence to deal with stigma issues, more freedom to pursue educational and business opportunities, and more time for family life, vacations and general social interaction.

In MMM, patients have greater freedom to travel since they report once per month. Therefore, patients are able to take extended vacations without the permission of the clinic. Also patients with jobs or careers that involve extensive travel are able to meet their obligations without relying on emergency approvals and travel arrangements to pick up methadone in other cities. They are able to change jobs more easily and work overtime or at odd hours without worrying about fixed clinic schedules. Also, patients were able to complete educational programs including advanced graduate degrees without the interference of frequent visits to a clinic. Patients were able to sustain careers in entertainment and law; operate and expand successful businesses in real estate, trucking, construction, jewelry, electronics, and antiques. Those with the proper skills and education obtained jobs in computer technology and business administration. Reporting monthly to a private physician as opposed to the regulated reporting schedules of the clinic was related by patients as a major advantage of MMM which permitted them the time and flexibility to achieve success in their endeavors. Most of the patients' college and graduate school education was completed when they were enrolled in methadone treatment, and advanced degrees were obtained more easily when the patients were enrolled in MMM. In addition to their regular monthly supply of methadone, MMM patients are permitted to have an additional five-day "insurance supply" of methadone in case of emergencies that would prevent them from keeping previously made physicians' appointments on specific reporting dates (e.g., inclement weather, deaths in the family, changes in physician's schedules, sudden illnesses, changes in business and working schedules, etc.). As in the practice of medicine with other conditions, reporting schedules in MMM are flexible to adjust to the requirements of the patients.

Thirty-seven of the 99 active patients also received adjustments in their methadone doses while in MMM. Twenty-seven patients received increases of 10 to 20 mg/d. Twenty-three of these patients reported that they were undermedicated in the clinics and experienced periodic withdrawal symptoms. They did not request increases in their doses for fear of losing privileges and reporting more frequently to the clinics. Four patients indicated that over the course of time in methadone medical maintenance treatment they felt that an increase in dose was indicated since they felt uncomfortable. Ten patients attempting to withdraw from methadone requested reductions in dose but the procedure was discontinued, since the patients felt that they needed to remain in treatment. These patients were restabilized at about 10 mg/d below the doses that they were stabilized on when they entered the program. Sixty-two patients did not request changes and remained on the doses that they were stabilized on in their clinics. In MMM, the prescribed dose is considered a medical rather than a regulatory matter, and appropriate changes are made by the physicians based on consultation with the patients.

Medical Problems and the Role of the Medical Maintenance Physician

In MMM, the patients receive greater attention to their medical problems compared to that received in traditional methadone clinics. The MMM program is staffed with specialists in internal medicine who assume responsibility as the patient's coordinator of primary health care. The internists have indicated that these compliant, rehabilitated methadone patients fit into their private practices as well as their other patients. The physicians have treated the MMM patients for various acute and chronic illnesses (e.g., asthma, hypertension, diabetes, coronary artery disease, bronchitis, AIDS, hepatitis C, ulcers, anxiety, depression, etc.) or have made referrals to other specialists. The program physician also acts, with the patient's permission, as an ombudsman for the patients by contacting and working with other specialists, informing them about methadone maintenance, its overall safety, the need for adequate pain management, and the applicability of continued MMM for the patients.

Tobacco-related illnesses are the leading cause of death in MMM, and the second most prevalent problem in active patients. Counseling concerning smoking cessation and the prescribing of nicotine replacements (e.g., patches and sprays), and bupropion are the major therapeutic efforts employed by the physician.

Hepatitis C is the most prevalent serious health problem affecting the patients. Eighty-five (92%) of the 92 patients tested positive for antibodies to hepatitis C virus-RNA (HCV-RNA). A detailed study of 84 patients who underwent confirmatory testing showed that 7 (8%) patients were antibody negative for hepatitis C RNA. Of the remaining 77 HCV-RNA positive patients, 24 (31%) had normal and 53 (69%) had elevated liver function tests. Polymerase chain reaction (PCR) tests administered to the 24 patients with normal liver function tests showed that HCV-RNA was not detected in 17 (22%) of the 77 patients. Of the 53 patients with elevated liver function tests and antibody positive for hepatitis C, 28 underwent biopsies as of 1998. Of the 28 biopsied patients, 20 were in treatment, 3 were formerly in treatment, and 5 were under observation. A study of the treatment environments at the time when the status of HCV RNA was determined (either positive or negative) for 46 patients, showed that 31 (68%) of the determinations were made in the MMM, 13 (28%) were made by private physicians and 2 (4%) were made in the traditional methadone clinics.

Four patients received liver transplants: three of the patients underwent successful operative and postoperative procedures. One of the patients died from an allergic reaction to a postoperative medication. However, one of the three surviving patients had to undergo a second transplant within three months due to hepatic decompensation with reactivation of hepatitis C. As stated previously, in the group of patients who were included in this report, hepatitis C ranked second as a cause of death within the MMM. Hepatitis C virus in methadone patients is reviewed by Novick elsewhere in this issue (18).

HIV/AIDs affected 3 patients (1.9%) all of whom died. One patient who stopped injection of heroin in 1971 acquired HIV from a sexual partner; the two other patients stopped injection at the beginning of the HIV/AIDS epidemic in 1978 and 1979. Of the 142 patients for whom there exists information on years of needle use, 103 (72%) report they stopped injection between 1964 and 1977, and the remaining thirty-nine (27%) stopped injection by 1987. By the 1980s Novick et al. reported that in studies in London, New York City, and Zurich, the prevalence of HIV was less than 10% among methadone patients who were in long-term treatment and who entered methadone treatment before the onset of increasing prevalence of HIV among drug injectors. In contrast, among untreated heroin addicts in New York City and in Zurich the reported prevalence of HIV infection was greater (58% and 36% respectively) (19).

A previous study of 58 patients from the early years of the MMM program described herein showed that none had antibody to HIV, but 53 (91%) had markers of hepatitis B virus infection. These patients had on the average 16 years of methadone treatment in traditional clinics prior to their admission to MMM. All abused heroin parentally for about 10 years prior to their admissions to methadone treatment. The high prevalence of hepatitis B markers suggests that patients used and shared needles prior to admission to treatment (20). However, during the course of the AIDS epidemic these patients were in methadone treatment and had terminated use of intravenous heroin. Therefore, none contracted HIV infection. Methadone-maintained patients who have engaged in high-risk drug use or sexual behavior after the onset of the HIV/AIDS epidemic are of course at risk for HIV infection.

Stigma Issues

The popular criticism of methadone maintenance treatment — that it just substitutes one addiction for another — trivializes the treatment, and ignores the extensive research and evaluations that show its effectiveness (21, 22). It also blurs the differences between methadone as used as a medication in maintenance and heroin as used in an extended addiction. Thus, the stigma of heroin addiction is transferred in modified form to methadone maintenance (21, 22). Therefore, methadone maintenance patients, especially those who are employed and socially stable, harbor an invisible stigma that affects every aspect of their lives (22). As reported previously in the literature, the decision to conceal or not to conceal their status as methadone patients is a primary consideration when they interact with members of their families, friends, co-workers, employers, and professionals from whom they receive services, including lawyers, physicians, nurses, teachers, and social workers (22, 23).

Most employed patients in the MMM have not used their medical insurance to pay for treatment. They fear that they may lose their jobs if their employers learn about their treatment, and therefore prefer to pay their physicians directly without reimbursement. While almost all MMM patients confide in their spouses, many will conceal their current enrollment in methadone treatment from children, parents, other relatives, and friends. In some instances, patients may tell their families about their previous heroin addiction, but not about their enrollment in methadone treatment.

Patients who see physicians not affiliated with the methadone program or who are hospitalized have refused to inform physicians and nurses about their methadone treatment out of fear that they will not be treated with respect, they will not receive proper pain management, and/or they will be withdrawn from methadone. Patients also refuse to inform people with whom they associate about their enrollment in methadone treatment, since routine fatigue may be misinterpreted as narcotization from methadone, and, as a consequence, they may be socially rejected (18).

Stigma, therefore, is the major social issue that confronts socially rehabilitated methadone patients (22, 23). While methadone medical maintenance does not remove stigma, the program has provided a better means to conceal enrollment and thus avoid the stigma associated with methadone maintenance (22). It also helps patients resolve internal doubts and shame about enrollment in the program so they can deal more realistically with social stigma.

Because of the stigma, misunderstandings and ignorance associated with addiction and methadone treatment, the prescribing physicians must be sensitive to stigma and confidentiality issues. The MMM physicians should help patients cope with stigma by educating them and their families about the nature of addictive disease, including the biological basis of methadone treatment and, where applicable, the need for continued methadone treatment.

Conclusions

MMM for a socially rehabilitated group of methadone patients is a viable alternative to treatment in the traditional methadone maintenance clinic system. It can be implemented within hospital-based medical practices of internists and general practitioners. For compliant patients, this program offers an opportunity for further improvements in their social lives, employment, and access to quality medical care. However, physicians must be trained about addiction and methadone maintenance treatment before accepting patients in private medical practice. Medical problems that socially rehabilitated methadone patients present can also be treated in addition to the prescribing of methadone.

In the program described, patients with alcohol and substance abuse problems were screened out by a selection process. The patients who remained had a greater incidence of medical problems related to years of smoking and intravenous addiction. The medical problems identified within this group of patients may be harbingers of some of the problems that will emerge within the younger clinic population of methadone patients as that population ages.

While in MMM, compliant patients have sustained or improved their employment situations, developed successful businesses, completed graduate and professional education, and maintained careers that include extended travel. It is the consensus of the physicians in the program that the behavior and personalities of the rehabilitated methadone patients in this program are similar to those of other patients treated by internists in private practice. Although a small group of compliant patients did manage to withdraw successfully from methadone treatment, a group of noncompliant patients did not succeed in the program for various reasons and had to be returned to their traditional clinics for continued treatment. The clinic system therefore functioned as a safety net for patients who were unable to abide by the regulations of the program.

Different models of MMM can be developed which are similar in concept to the one described in this article but which may differ in administrative structure. To ensure that standards are maintained, evaluations of new models should be undertaken. Federal, state and local regulations should be modified to encourage the development of MMM. A major limiting factor in the expansion of MMM is the recruitment of trained physicians and nurses. Training, education and nonbiased attitudes are essential if methadone patients are to be effectively treated.

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Effects of LAAM and Methadone Utilization in an Opiate Agonist Treatment Program

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Abstract

The development and approval of levo-alpha-acetylmethadol (LAAM) as a pharmacotherapeutic agent in opioid agonist therapy provided an alternative to methadone. Clinicians recognized the potential benefits that LAAM, a synthetic mu agonist with pharmacological properties which differ from those of methadone, could have in the treatment management of addicts in opioid agonist therapy. We report our experience utilizing LAAM from 1995 to 1999 at the Hines VA opioid agonist therapy clinic. The addition of LAAM to the clinic's treatment armamentarium has resulted in management options that have improved the areas of patient recruitment, patient retention, patient traffic, take-home medication, detoxification, and treatment outcomes.

Key Words: LAAM, methadone, opiate addiction, opioid replacement therapy.

Introduction

SINCE ITS INTRODUCTION, opioid agonist therapy has been shown to be effective in the treatment of opiate addiction. (1). The synthetic mu agonist methadone has been the primary agent used for this treatment modality. Its 24–36 hour half-life and oral administration made it an ideal agent when compared to the shorter half-life opiates. Numerous subsequent studies have shown treatment with methadone to be a cost-effective manner of decreasing illicit opiate use (2, 3), improving social functioning (4, 5), decreasing associated criminality (2, 6, 7), and improving public health (8–11).

In the past 35 years since methadone was first used in opioid agonist therapy, long-term, high-dose methadone maintenance therapy has been shown to be most beneficial to the chronic opiate addict. As a result of such obstacles as regulatory pressures, stigma associated with methadone treatment, methadone diversion fears, and initial daily clinic attendance requirements, only 20% of the opiate addicts who need treatment actually access the opioid substitution clinics (3), despite their proven efficacy. These factors, along with the fact that methadone fails to stop illicit opiate use in approximately 45% of patients, have fueled the search for additional pharmacotherapeutic replacement agents.

Levo-alpha-acetylmethadol (LAAM) has been shown to be an effective opioid agonist pharmacotherapeutic agent, comparable to methadone, for decreasing illicit opiate use, improving social functioning, decreasing criminality and improving public health (12–15). Most recently, results of a meta-analysis of randomized controlled trials comparing LAAM to methadone in treating heroin addiction showed no difference in the level of illicit drug use. There was, however, a small but statistically significantly greater patient retention rate in the methadone group, and discontinuation of treatment because of side effects of LAAM also favored methadone (16). The authors noted that the differences in retention rates might not be due entirely to the pharmacological properties of the replacement agents. Staff and patient factors, as well as the novelty of LAAM coupled with the familiarity of methadone, influence retention rates. In many of the clinical trials, LAAM patients could return to methadone, if they no longer wished to take LAAM. Meta-analysis supports LAAM as an effective alternative to methadone in the treatment of heroin addiction.

LAAM was approved for use as an opioid agonist medication by the Food and Drug Administration (FDA) in 1993. In 1995, the Center for Substance Abuse Treatment (CSAT) of the Substance Abuse and Mental Health Services Administration (SAMSHA) issued Treatment Improvement Protocol (TIP) #22, summarizing the clinical and basic research on LAAM, with guidelines for patient selection, induction of patients on the medication, dosing, stabilization, and ongoing maintenance.

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Initial recommendations for dosing and administration schedules for LAAM were proposed following research trials involving more than 4,000 patients (12–18). Dose-related efficacy for LAAM has been demonstrated, by Eissenberg et al. (19), who showed higher treatment retention rates and lower illicit opioid use relative to pre-treatment levels when LAAM dosing regimens of 100/100/140 mg (high-dose group) were compared to those of 50/50/70 mg (medium-dose group) and 25/25/35 mg (low-dose group).

The primary pharmacological differences between LAAM and methadone that make LAAM a positive addition to opioid agonist therapy include the production of active metabolites during liver metabolism and half-lives for the active compounds ranging from 2–4 days. These properties result in adequate levels of active narcotic compounds to suppress the dependence syndrome and maintain a "blockade" of the opiate receptors despite fewer doses per week than with methadone. The reader is referred to more extensive papers of the pharmacological properties of the agents currently in use for opioid replacement therapy (20–22). The main purpose of this paper is to relate the effects of LAAM utilization in everyday clinical practice. The ability of the long half-life mu agonists (LAAM and methadone) to develop "quality tolerance," as compared to the short half-life mu agonists (heroin, morphine, etc.), and its importance in opioid replacement treatment is also discussed.

Quality Tolerance

The concept of what we have termed "quality tolerance" has provided us with a theoretical framework for understanding the effects, benefits, and disadvantages of methadone, LAAM, and the short-acting narcotics in opioid substitution. Although partly speculative, it is meant not only to provide a theoretical framework, but also to promote further work in the concept.

Tolerance can be defined as loss of or diminished effect, of a given amount of drug in an individual. It is an adaptation of the target site of action to the continuous presence of a foreign substance, such as an opioid. The adaptation probably occurs at the receptor level, mediated by receptor-opioid interactions. The opiate receptor and opioid pharmacokinetic and pharmacodynamic properties determine the level and quality of adaptation (tolerance).

The half-life of the agent is an important factor determining the tolerance produced; the longer the half-life, the better the "quality tolerance." "Quality tolerance" allows the opioid agonist patient to function. Opioid agonist benefits would not be possible without the ability of methadone and LAAM to produce "quality tolerance." The short half-life agents produce little if any clinically significant "quality tolerance." The difference in the ability to produce "quality tolerance" between methadone, LAAM and the short half-life opiates results in the following: (a) limited benefit of short half-life agents in opioid agonist treatment, (b) the need to induce a patient onto methadone or LAAM despite years of abusing the short-half life opiates, (c) a more normal feeling with LAAM maintenance than with methadone maintenance.

LAAM and its two active metabolites, nor-LAAM and dinor-LAAM, produce an equilibrium state at the receptor level, characterized by prolonged occupation of the mu receptors. Methadone also produces such an equilibrium, but to a slightly lesser extent than LAAM. Short half-life agents would not produce such an equilibrium. Their use actually sets up a disequilibrium state, as the addict fluctuates from a peak to a rapidly decreasing level of opiate with each use. This disequilibrium seems to fuel the addictive process, as clinically manifested in the compulsion and craving that a heroin addict exhibits. LAAM and methadone, on the other hand, decrease the compulsion and craving as a result of the equilibrium they establish and the "quality tolerance" that then develops. The decrease in compulsion and craving is likely to be the clinical reflection of the neuronal system responsible for the addictive process, i.e., re-stabilizing. This re-stabilization leads to a successful treatment outcome, i.e., stopping or reducing the use of illicit opiates. The establishment of an equilibrium in opioid agonist treatment arrests the addictive disorder, much like the abstinent equilibrium of the abstinent treatment approach.

We will refer to the concept of "quality tolerance" and the theoretical framework outlined above at various points during presentation of our experience utilizing LAAM.

Induction

We have placed patients on LAAM in one of two ways:

1) An established methadone maintenance patient can be converted directly to LAAM. The 48-hr dose of LAAM is obtained by multiplying the daily methadone dose by 1.2. The fact that the "quality tolerance" produced

by methadone is near the level of that produced by LAAM allows conversion from methadone to LAAM and vice versa without any need for re-stabilization. The conversion is clinically equivalent.

In patients with rapid liver metabolism maintained on methadone doses greater than 100 mg per day, the first dose of LAAM should not exceed 120 mg/48 hr. This rule is needed since liver metabolism of methadone results in inactive metabolites whereas liver metabolism of LAAM results in active compounds. Converting such a patient to LAAM using the 1.2 conversion would result in too high a LAAM dose. Our experience has been that this patient may require an increase or decrease in the range of 10 – 15 mg from their initial dose of 120 mg/48 hr. The production of active metabolites has made LAAM our preferred method of managing a rapid metabolizer that cannot be stabilized despite doses of methadone well beyond 100 mg per day. Conversion of such a patient to LAAM will allow stabilization and bring the dose of agent to normal ranges.

The equivalency of the conversion is an important fact since it has provided us with the ability to dose a patient for 24 hrs, 48 hrs, or 72 hrs, whether they are on methadone or LAAM. The only thing that cannot be done is to give LAAM on sequential days; all other combinations of LAAM and methadone are possible. The benefits of combining LAAM and methadone are most apparent in the management of take-home doses of methadone. This is discussed in more detail later in this article.

2) A patient can also be placed directly on LAAM from illicit street opiates. In this case, an induction is necessary, since the illicit short half-life opiates do not produce any significant amount of "quality tolerance." This is our preferred method of inducing a patient. We do not utilize the technique of inducing a patient onto methadone first, reaching an adequate dose of methadone, and then converting to LAAM. We found that this method is unnecessary, cumbersome, and without significant advantages over direct rapid induction onto LAAM.

We begin with a 30 mg/48 hr dose of LAAM. We then increase the dose by 5 – 10 mg increments each time the patient comes to dose, with the minimal target dose being 75 mg/48 hrs. If sedation occurs in an individual patient, using smaller incremental increases in the dose or increasing the interval between increases can slow induction. Our experience has been that the majority of patients tolerate the rapid induction technique. Furthermore, the rapid induction method is important in alleviating patients' withdrawal symptoms, increasing retention and improving outcome.

We prefer to have at least three 48-hr LAAM doses before giving a patient being induced a 72-hr dose of LAAM. This prevents any significant sedation with the larger 72-hr dose (quality tolerance better developed), and assures better coverage for the 72-hr period. We use the 72-hr dose since we are a 6-day per week clinic. LAAM 48-hr doses and equivalent methadone doses can be used to shift the patient's dosing schedule to a desired day of the week prior to using a 72-hr dose.

An example of what we have termed "phase shifting" is the case of a patient who is admitted on Monday in moderate withdrawal. The decision is made to place the patient on a Monday/Wednesday/Friday schedule of LAAM (a Tuesday/Thursday/Saturday schedule is also possible), but we want to give him more than two 48-hr LAAM doses (Monday and Wednesday) prior to the 72-hr dose (Friday). We would give this patient a 30-mg dose of methadone on the Monday he was admitted — first shift — then he would get LAAM 30 mg/48 hr on Tuesday, 40 mg/48 hr on Thursday, 50 mg/48 hr on Saturday — second shift — 60 mg/48 hr on Monday, 70 mg/48 hr on Wednesday, and 112 mg/72 hr on Friday. This Monday/Wednesday/Friday dosing schedule would be maintained for at least a month in order to reach steady state. During this interval, we would have the opportunity to counsel the patient, and determine if illicit opiate use ceases. We increase the dose if illicit opiate use continues. Similar examples of "phase shifting" can be generated for patients admitted on different days of the week and/or placed on a Tuesday/Thursday/Friday dosing schedule, the goal being at least three 48-hr LAAM doses prior to a 72-hr dose.

Maintenance

We have found that, as a group, patients maintained on doses below 95 mg/48 hrs have greater rates of opiate-positive urine toxicologies as compared to patients maintained on doses above 95 mg/48 hrs. This is consistent with Eissenberg's randomized clinical trial (19). It has been uncommon in our clinic for patients to require 48-hr LAAM doses above 140 mg.

Dosing Regimens and the 72-hr Dose

LAAM can be dosed every 48 hrs or three times per week. The latter method requires two 48-hr doses and one 72-hr dose. We have used the three times per week dosing regimen exclusively, and have not found it necessary to supplement this regimen with a methadone take-home dose. We are aware that some clinics use a three time per week dosing schedule that gives a patient two 48-hr doses of LAAM with coverage for the 72-hr period carried out with a 48-hr dose of LAAM and a take-home dose of methadone for the third day. The latter method is unnecessary if the increase in LAAM dose for the 72-hr period is calculated correctly.

We give an additional 40% amount of LAAM for the 72-hr period as compared to the 48-hr period. A patient on a 48-hr LAAM dose of 100 mg will get a 72-hr LAAM dose of 140 mg. This results in adequate coverage for the 72-hr period for the large majority of patients (95%). The other 5% of patients in our clinic have noted that the increase for the 72-hr period made them feel "heavy" on the first day. These patients can be given a lower increase the next time a 72-hr dose is calculated (30%, rather than 40%). If a clinic calculates the 72-hr dose using less than 40%, a proportional number of patients will complain of "not being held" on the third day, and implementation of LAAM utilization will be compromised. Opioid replacement patients tend to reject an agent that does not provide adequate coverage from the beginning, and they are less likely to accept the argument that all that may be needed is an increase in dose. We strongly recommend that an increase of 40% be used initially for calculating the 72-hr dose of LAAM.

The advantages that our clinic has seen as a result of the three times per week LAAM dosing have been:

1) Avoids need for methadone take-home doses for LAAM patients.

2) Increases our clinic patient capacity since we are able to: (a) decrease the number of weekly doses per patient on maintenance, (b) decrease patient traffic since we can have M/W/F and T/Th/Sat LAAM patients, and (c) relieve counselor workload by having a part of their patient caseload come to the clinic only three times per week.

Our clinic was able to double its census without an increase in drug dispensing or counselor resources in part because of these advantages.

The advantages of the three times per week dosing makes it the preferred method, even in 7-day-per-week clinics. Dosing days for a given patient remain the same and do not change each week as they would with a regimen that uses 48-hr doses only.

Patient Selection

We have used LAAM for the following patients:

1. Those desiring less frequent visits to the clinic from the beginning of treatment.

2. Those who had not done well on methadone maintenance despite doses of methadone above 60 mg per day. We converted 37 patients that continued using illicit opiates to LAAM. The average methadone dose in this group of patients was 66 mg. The LAAM dose was obtained by using the conversion factor of 1.2. No dose increases of LAAM were made following the conversion. At 6 months, 87% of the patients were still in treatment, and 83% of these patients had stopped using illicit opiates. LAAM should be tried with those patients who have not done well on methadone.

3. Those suspected of diversion. Diversion is prevented, daily clinic attendance is avoided, and patient retention is increased.

4. Those desiring confidentiality regarding their participation in substitution treatment, since LAAM is not routinely tested for in commonly used toxicology screens. In our clinic, this has helped us retain patients who contemplated leaving treatment because they did not want their employers to know they were on methadone for fear of either losing their job or not getting desired jobs. In the past, these patients would have detoxified and, more often than not, would have relapsed to illicit opiate use.

5. Those experiencing too much sedation with methadone maintenance, due to LAAM's

greater "quality tolerance" and more normal feeling. This has been helpful in managing patients who have jobs operating machinery and who experience significant sedation after dosing with methadone.

6. Those with absenteeism problems, with a drug that is dosed less frequently.
7. Those who are medically and/or cognitively compromised. This avoids daily visits to the clinic and reduces the need for take-home medication for which they may not be completely responsible.
8. Those who are "rapid metabolizers," as previously mentioned.

The expanded patient selection options have been particularly helpful in improving our retention rates, access to treatment, and ultimately our clinic census. These options are among the factors that have allowed us to increase and maintain our census at twice the level of that prior to the utilization of LAAM.

Improved Take-Home Dose Management

We have combined the use of LAAM and methadone to improve management of methadone for methadone-maintained patients who report from Monday to Saturday.

In our clinic, patients who are maintained on daily methadone from Monday to Friday, since they have not qualified for methadone take-home doses, are given an equivalent 48-hr dose of LAAM on Saturday. They are given their regular dose of methadone when they return to the clinic on Monday. This avoids the previously routine Sunday take-home doses of methadone. We have done this for nearly two years and have had no major problems. A comparison between the period of time covered with methadone and the period of time covered with LAAM shows no significant differences in withdrawal symptoms, drug craving, and drug use history (23). Past attempts to use this technique by other investigators did not succeed primarily because of low dose of LAAM given (24).

The above technique could allow a clinic which must remain open 7 days per week because of regulations preventing Sunday take-home doses, to close on Sunday without the need to give a take-home dose of methadone.

One- or two-day coverage during the week can be provided to a methadone-maintained patient by converting to an equivalent 48-hr or 72-hr LAAM dose, respectively. This has been helpful in our clinic as an alternative to methadone take-home doses for short-term personal and/or medical hardship requests by patients who have not qualified for take-home privileges.

Improved Overall Clinic Treatment Outcome

Utilization of methadone and LAAM improved the rate at which our patients succeeded in achieving opiate-free status. This success was defined as negative urinalysis for illicit opiates for the previous three months following at least six months of treatment. Prior to introducing LAAM to our clinic at the end of 1995, we had 125 patients in methadone maintenance, and our rate of heroin-free status was 55%. Two years after the introduction of LAAM, our census was 250 patients, 2/3 on methadone and 1/3 on LAAM. The rate of heroin-free status had improved by 12% to 67%. The methadone-maintained group had a heroin-free rate of 60%, while the LAAM-maintained group had a heroin-free rate of 80%.(25). These statistics suggest that improved treatment-patient matching might have resulted from the availability of two opioid agonist agents. The 12% improvement supports the utilization of available agents for opioid agonist treatment.

Detoxification

The 2 – 4 day half-lives of LAAM and its active metabolites, nor-LAAM and dinor-LAAM, suggests that the intensity of withdrawal symptoms after discontinuation would be less intense for LAAM than for methadone, which has a half-life of 24 hrs. The slower clearance rates of LAAM and its active metabolites attenuate withdrawal symptoms. A double-blind comparison of gradual and abrupt withdrawal from LAAM (25) suggested that intensity of withdrawal symptoms due to discontinuation of LAAM might be helpful in detoxification.

LAAM-maintenance patients in our clinic detoxify from LAAM by decreasing their 48-hr dose by 4 mg each time they are dosed. When a 40 mg/48 hr dose is reached, we slow the detoxification to a 3-mg decrease each time they are dosed. When a 20 mg/48 hr dose is reached, we complete the detoxification by 2-mg decreases each time they are dosed. More important, if we have a patient who has failed detoxification from methadone maintenance as a result of symptom intensity, when lower doses are reached, we like to convert them to LAAM if and when they ask to detoxify from methadone. Some of these patients have been able to complete the detoxification. LAAM should be evaluated further for use in detoxification from opiates.

Side Effects

We have found the side effect profile of LAAM to be similar to that of methadone. This is not surprising since they are both mu agonists. The most common and lasting side effect of LAAM in our clinic has been constipation. Sexual dysfunction, nervousness, and sweating have occurred at rates and intensity similar to those for methadone.

We have used LAAM without complications in patients with hepatitis C and alcoholic hepatitis. Our clinical experience suggests that if a patient can be given methadone, LAAM can also be tolerated. Further work is needed on the use of opioid replacement agents in special populations.

We have not found that LAAM poses any greater danger than does methadone for a patient who abuses other illicit drugs. Unfortunately, we have not noticed any significant difference in the use of cocaine or benzodiazepines between patients on LAAM and those on methadone maintenance.

Conclusion

The utilization of LAAM and methadone in our clinic has increased the options available to us for the management of our patient population. Access to treatment, patient retention in treatment, and positive treatment outcome have consequently increased. Our clinic experience supports the expansion of LAAM utilization in opioid agonist therapy.

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When "Enough" Is Not Enough:

New Perspectives on Optimal Methadone Maintenance Dose

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Abstract

Some methadone maintenance treatment (MMT) programs prescribe inadequate daily methadone doses. Patients complain of withdrawal symptoms and continue illicit opioid use, yet practitioners are reluctant to increase doses above certain arbitrary thresholds.

Serum methadone levels (SMLs) may guide practitioners' dosing decisions, especially for those patients who have low SMLs despite higher methadone doses. Such variation is due in part to the complexities of methadone metabolism. The medication itself is a racemic (50:50) mixture of 2 enantiomers: an active "R" form and an essentially inactive "S" form. Methadone is metabolized primarily in the liver, by up to five cytochrome P450 isoforms, and individual differences in enzyme activity help explain wide ranges of active R-enantiomer concentrations in patients given identical doses of racemic methadone.

Most clinical research studies have used methadone doses of less than 100 mg/day [d] and have not reported corresponding SMLs. New research suggests that doses ranging from 120 mg/d to more than 700 mg/d, with correspondingly higher SMLs, may be optimal for many patients.

Each patient presents a unique clinical challenge, and there is no way of prescribing a single best methadone dose to achieve a specific blood level as a "gold standard" for all patients. Clinical signs and patient-reported symptoms of abstinence syndrome, and continuing illicit opioid use, are effective indicators of dose inadequacy. There does not appear to be a maximum daily dose limit when determining what is adequately "enough" methadone in MMT.

Key Words: Methadone, therapeutic dose, serum methadone levels, pharmacokinetics, metabolism, clinical implications.

Introduction — Shaping Clinical Intuition

Patients in methadone maintenance treatment (MMT) programs frequently complain of withdrawal symptoms and continue their high-risk behaviors. They protest, "My dose isn't holding me"; "I have drug cravings at night"; or "I wake up sick every morning" (1). Yet practitioners may be reluctant to increase methadone doses above certain thresholds, believing patients are already receiving "enough" of the medication (1). Payte and Khuri (2) have defined "enough" methadone as "the amount required to produce the desired response for the desired duration of time, with an allowance for a margin of effectiveness and safety." However, the issue of optimal methadone dosing during maintenance therapy — what is "enough" under various circumstances — still seems unresolved.

Vincent Dole, a co-developer of MMT in the mid-1960s, advised that (3) "there is no compelling reason for prescribing doses that are only marginally adequate. As with antibiotics, the prudent policy is [to] give enough medication to ensure success." However, MMT programs may prescribe inadequate daily doses of methadone more for philosophical, moral, or psychological reasons than for sound pharmacological and clinical ones (4). Many clinicians also assume that lower doses automatically prevent toxicity and eventually engender opioid abstinence (5).

Some researchers have recommended routine therapeutic drug monitoring using serum methadone levels (SMLs) as a diagnostic tool for guiding dosing decisions (4), and have noted a correlation between "poor performance" in MMT and lower methadone serum levels (6). Others have concluded that the determination of such serum levels is not likely to be of practical value in MMT programs (7), and that many patients

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have subtherapeutic SMLs despite "high" methadone doses (7, 8).

There are indications that SMLs can be useful when the clinical picture does not agree with the typical or expected response to a given dose of methadone (1), but they must be used and interpreted cautiously. Regardless of a particular serum level reading, the patient may not be getting enough daily methadone (9). Clinical signs and patient-reported symptoms of abstinence syndrome and illicit opioid use can often be the most effective indicators of dose inadequacy.

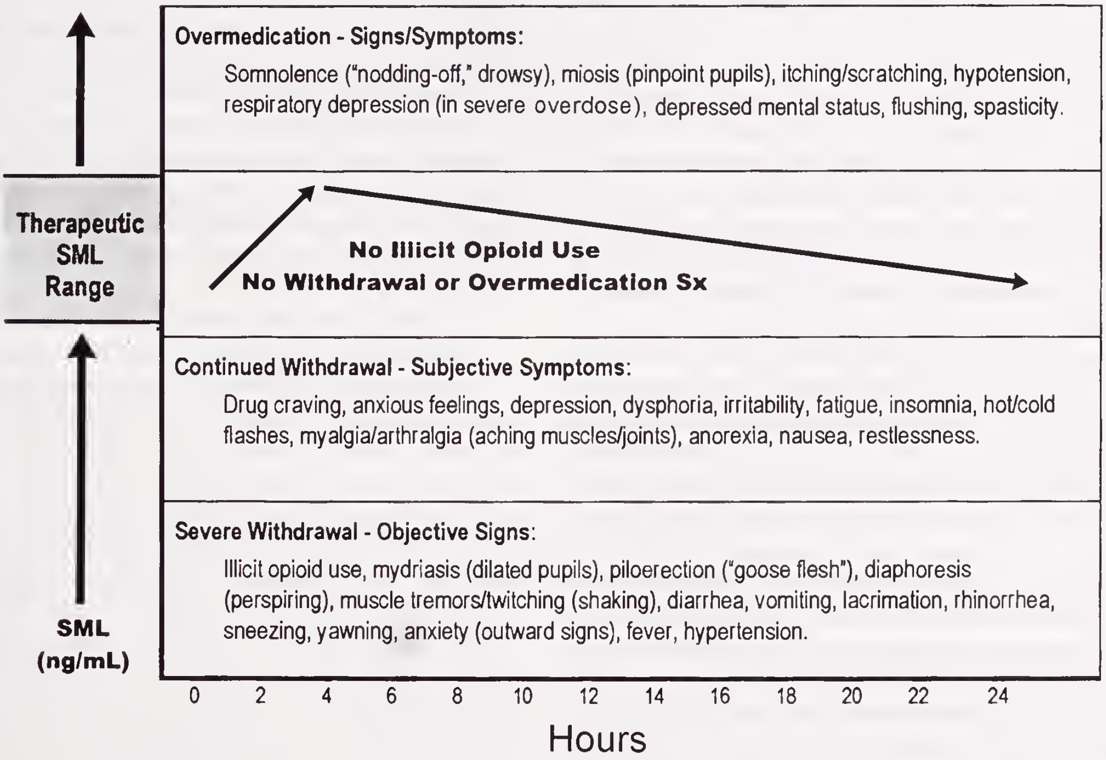
For several reasons discussed in this paper, higher methadone dosing and correspondingly higher SMLs than previously considered necessary or advantageous may be desirable. An understanding of methadone's pharmacokinetics and pharmacodynamics can enhance clinical intuition and assist practitioners in prescribing reliably effective and safe doses that will result in better MMT outcomes.

Traversing Peaks and Troughs

Methadone, administered daily at a steady dose, should be present in the blood at levels sufficient to maintain an asymptomatic state over a 24-hour period, with no periods of opioid overmedication or withdrawal (1, 4). As with any opioid, methadone withdrawal (abstinence syndrome) involves a constellation of clinical signs and symptoms (2, 3, 9, 10–12) (see Table 1). It is important to note that patients may experience subjective symptoms in the absence of observable signs (3), and the onset and severity of withdrawal in methadone-maintained patients are variable, depending on the patient's metabolism of the medication, among other factors.

Table 1

Signs/Symptoms of Opioid Withdrawal (Abstinence Syndrome) and Overmedication (2, 3, 9-12)



Overmedication - Signs/Symptoms:

Somnolence ("nodding-off," drowsy), miosis (pinpoint pupils), itching/scratching, hypotension, respiratory depression (in severe overdose), depressed mental status, flushing, spasticity.

Continued Withdrawal - Subjective Symptoms:

Drug craving, anxious feelings, depression, dysphoria, irritability, fatigue, insomnia, hot/cold flashes, myalgia/arthralgia (aching muscles/joints), anorexia, nausea, restlessness.

Severe Withdrawal - Objective Signs:

Illicit opioid use, mydriasis (dilated pupils), piloerection ("goose flesh"), diaphoresis (perspiring), muscle tremors/twitching (shaking), diarrhea, vomiting, lacrimation, rhinorrhea, sneezing, yawning, anxiety (outward signs), fever, hypertension.

SML+ serum methadone level
As the serum methadone level rises, the objective signs of abstinence syndrome disappear and the clinician uses subjective symptoms as a guide for further dose increases. At the optimal methadone dose, the serum methadone level stays in the therapeutic range throughout the 24 hour period. If the methadone dose is too high, signs/symptoms of overmedication appear

The elimination half-life of methadone averages 28 hours or less, but may range from as low as 4 hours to a high of 91 hours. The clearance rate of methadone from the body can vary from individual to individual by a factor of almost 100 (5, 13). Measuring levels of methadone in the blood via SMLs — in nanograms per milliliter (ng/mL) — is helpful in determining just how much of the medication is circulating in the patient's system at the time of testing. Typically, the blood level reaches a high point, or "peak," about 3 to 4 hours after taking the dose, and there is a gradual decline over the remainder of the 24-hour period to a low point or "trough" level before the next dose (1). Although a strong correlation between methadone dose and concentrations in plasma ($r = 0.82$, $p < 0.001$) has been noted (14), the relationship may not be linear. Moreover, there is a need to account for the high degree of inter-individual variation (5, 15–17).

Payte and Zweben have suggested (1) that the peak SML at 3 to 4 hours post-dosing should be no more than twice the trough level, giving an ideal peak/trough ratio of 2 or less. A trough SML alone, although of some use, does not indicate the rate at which the serum level changes over the time-course of a dose (1). However, in everyday clinical practice, measuring peak and trough levels can be time-consuming and invasive, due to necessary multiple phlebotomies (5). In lieu of this, physically evaluating patients for signs/symptoms of overmedication (Table 1) about 3 hours after a dose increase can help to assess whether the peak/trough ratio is appropriate (16).

Researchers have affirmed the need for a trough SML of 150–600 ng/mL to suppress drug craving (1, 3, 4), and a trough level at or above 400 ng/mL to provide adequate opioid cross-tolerance which makes ordinary doses of IV heroin ineffective (non-reinforcing) during MMT (1, 2). Today, many practitioners consider an SML of 400 ng/mL (trough) as adequate therapy for stabilized methadone maintenance. However, Eap et al. (13) have observed that "no study so far has clearly demonstrated the existence of such a threshold [i.e., minimally adequate SML]," and Hiltunen and colleagues (10) noted that recommended SML ranges have not been validated against self-reported clinical symptoms in patients. An optimal trough SML may range from 400 mg/mL to values much higher, and efforts to set methadone ceiling doses and commensurate SMLs by policy or regulation are not based on scientific, clinical, or laboratory evidence (1).

Broad SML Ranges

Patients taking the same methadone doses have SMLs which vary significantly. Bradbury and Paris reported on 55 patients evaluated for ongoing problems with their methadone dose and opiate withdrawal signs/symptoms (15). Average patient time in treatment was 46 months and mean methadone dose was 98 mg/d (range 30–160 mg; mode 100 mg). Trough methadone plasma levels were obtained for all patients upon entry into the study (Table 2).

SMLs ranged from 10–530 ng/mL, with some patients well below adequate trough levels at each methadone dose. Moreover, as Table 2 demonstrates, there was no apparent correlation between methadone dose and SML. More than a third of the patients also were being prescribed psychotropic medications — e.g., antipsychotics, antidepressants, benzodiazepines, anticonvulsants — and this was positively correlated with continued opioid abuse. The authors speculated that there may be limitations in the psychosocial coping mechanisms in such patients influencing continued opioid abuse (15). However, as others have found, there could also have been metabolic interactions of methadone with the prescribed psychotropic medications, and SMLs below therapeutic thresholds for those particular patients (1, 9, 13, 18).

SMLs are generally more appropriate for confirming inadequate dose than for determining the optimum dose, and they should be interpreted within the context of the patient's overall clinical presentation. Bradbury and Paris provide some telling examples (15):

> A woman transferred from an MMT program where she was having difficulties but was told that her 100 mg/d dose was "enough." At the

TABLE 2

MMT Patients Evaluated for Dose/Withdrawal Problems (15)

n	Dose mg/d;	SML — mean ± (SD) mg/mL	SML — range ng/mL
2	30	70 (42.4)	40–100
1	40	20	—
1	50	320	—
4	60	95 (65.6)	10–170
4	70	132.5 (58.5)	100–120
4	80	332.5 (205.7)	150–530
1	90	350	—
20	100	236.4 (122.4)	90–520
2	110	115 (134.4)	20–210
10	120	212.4 (142.4)	10–440
3	140	271.2 (123.6)	130–360
3	160	243.3 (181.5)	50–510

> new clinic her dose was raised to 120 mg/d but the plasma level was still fairly low (130 ng/mL). The dose was titrated upward to 180 mg/d, relieving her withdrawal symptoms.
>
> A patient taking several psychiatric medications and 80 mg/d of methadone was experiencing severe withdrawal symptoms. Her trough SML was non-detectable. However, at 140 mg/d she experienced sedation soon after taking her methadone, and opiate withdrawal at night (peak/trough ratio apparently high). Splitting the dose — 70 mg in the morning and 70 mg at night — eliminated both sedation and withdrawal symptoms.
>
> A male patient was stable and free of illicit drugs at 100 mg/d, but insisted on a dose reduction. At a lower dose he soon developed withdrawal symptoms. His blood level tested at 100 ng/mL, convincing him he needed to return to the original dose.

As in the last example, many patients have concerns about needing higher methadone doses and may minimize reported withdrawal symptoms or deny the extent of continued opioid abuse. SMLs can be used as a tool to address those fears, objectively demonstrating when the dose is too low to provide an adequate therapeutic blood level of the medication. And for patients taking co-medications or with organic dysfunctions such as liver or kidney disease, which might interact with methadone metabolism, SMLs can help confirm a need for higher dosing or split doses to achieve desired therapeutic levels (15).

Nuances of Methadone Metabolism

Methadone's peak-trough-average SMLs and its rate of elimination (half-life) may be influenced by several factors, such as poor absorption, metabolism, changes in urinary pH, concomitant medications or drug abuse, diet, physical condition, pregnancy, and even vitamins (1, 15, 18). Considerable flexibility in dosing is required to stabilize patients whose methadone pharmacokinetics may be affected by so many factors.

Methadone itself is a more complex substance than many appreciate. The formulation universally used in MMT is a 50:50 racemic mixture of two molecular forms, or enantiomers, specified as "R" (also called *levo-* or *l-methadone*) and "S" (*dextro-* or *d-methadone*). These two enantiomers have the same chemical composition but different spatial arrangements and kinetics: only R-methadone has clinically significant mu-receptor agonist activity, while the S form is essentially inactive as an opioid agonist. R-methadone also has a higher clearance rate (13).

These differences in methadone structure and action have been known since the earliest days of MMT. In their original 6 patients, Dole (3) tried switching from the usual racemic R/S mixture to S-methadone and noted the gradual appearance of abstinence symptoms. Unaware of the switch, patients reported that they "seemed to be getting the flu." When returned to a mixture also containing the R-enantiomer, the patients again became functionally normal.

Methadone metabolism is largely a function of liver enzyme activity involving cytochrome P450 isoforms (CYP450 enzymes). Drugs that induce these enzymes can accelerate methadone metabolism, abbreviate the duration of its effect, lower the SML, and precipitate abstinence syndrome. Other drugs can inhibit this enzyme activity and slow the rate of methadone metabolism, thereby raising the SML, and extending the duration of methadone's effects (1, 13).

Recent research has demonstrated that several CYP450 isoforms — CYP3A4, CYP2D6, and to a smaller extent CYP1A2, and also possibly CYP2C9 and CYP2C19 — are involved in methadone metabolism (13, 19). Eap and colleagues have reported on genetic and environmental factors acting on these enzymes, leading to a high degree of inter-individual variation in methadone pharmacokinetics (13).

First, the CYP2D6 isoform selectively metabolizes the R-methadone enantiomer. A genetic polymorphism has been described for this enzyme, which is virtually absent in a small portion of the population, resulting in decreased metabolism of methadone. Another segment of the population has very high CYP2D6 activity due to duplication or multiplication of the CYP2D6 gene, and such persons might require very high SMLs of methadone for optimal effect, since there is an increased metabolism of the active R-enantiomer (13).

Second, there is more than a 40-fold inter-individual variation in activity of the CYP1A2 isoform, although it is not genetically polymorphic. CYP1A2 appears to be involved in metabolizing both R- and S-methadone but, overall, plays a relatively minor role. Of interest, tobacco smoking enhances the enzyme's activity, leading to faster methadone metabolism (13, 17).

Third, CYP3A4, the most abundant CYP isoform in the liver, is also expressed in the gut. While there is no genetic polymorphism, there is up to a 30-fold inter-individual variability of its existence and activity in the liver, and up to an

11-fold variability in the gut. CYP3A4 is also involved in the metabolism of many medications, such as selected benzodiazepines, antidepressants, anticonvulsants, antibiotics, and antivirals (including interferon and HIV protease inhibitors), that MMT patients may be taking. These and others can interact to raise or lower the methadone SML (see Table 3). In some cases, such as when MMT is initiated, methadone itself may induce increased CYP3A4 activity (13).

Finally, a very recent *in vitro* study suggests that two other CYP enzymes — CYP2C9 and CYP2C19 — may be involved in methadone metabolism (19). However, their relative clinical importance still needs confirmation by *in vivo* investigations.

In sum, individual differences in the activity of CYP1A2 and CYP3A4, in addition to the genetic polymorphism of CYP2D6 and the possible involvement of CYP2C9 and CYP2C19, help account for wide variances in methadone metabolism. As a result, in patients given exactly the same dose of racemic methadone, corrected for body weight, concentrations of the active R-enantiomer can vary from 1- to 17-fold even in the absence of potentially interacting co-medications (13). Such phenomena help explain clinical cases of so-called "fast metabolizers" who repeatedly complain, "My methadone dose is not enough to hold me."

The Glass Ceiling

Past research over the years raises the question: How high is a "high" methadone dose? Dole observed long ago (3) that 100 mg/d may fail to hold methadone blood levels within a therapeutic range for many patients. Despite this, a 100-mg dose has become accepted as a "glass ceiling" of sorts, rarely to be penetrated, and in practice much lower thresholds are maintained.

TABLE 3

Some Drugs That Affect Methadone Metabolism (1, 2, 18)*

↓ Reduce SML**	↑Increase SML
Phenytoin	Cimetidine
Carbamazepine	Ketoconazole
Rifampin	Fluconazole
Barbiturate sedatives/hypnotics	Amitriptyline
Certain antivirals	Diazepam
Urinary acidifiers, ascorbic acid	Fluvoxamine maleate
Ethanol (chronic use)	

Contraindicated Drugs — Precipitate Opioid Withdrawal
Opioid antagonists (naloxone, nalmefene, naltrexone), tramadol, buprenorphine, butorphanol, dezocine, nalbuphine, pentazocine

*Note: List is not inclusive of all drugs that may interact with methadone

**SML=serum methadone level

An extensive survey conducted in 1988 by the University of Michigan Institute for Social Research found that nearly 70% of U.S. clinics maintained patients at an average dose of 50 mg/d or less (20). This was well below an 80–120 mg/d range recommended by Dole and others (1–3, 21), which would average about 100 mg/d, with significant numbers of patients above and below the range. This situation seems to have improved only slightly since 1990, as informal surveys found that the U.S. average methadone dose was 56.6 mg/d in 1993 and 69.4 mg/d in 1998 (22).

Clinical researchers continue to evaluate low methadone doses. Although several often-quoted studies found that "higher" doses were more beneficial in terms of less continued opioid abuse, the doses studied averaged only in the 40–50 mg/d range (23–25). One randomized trial explored the relative merits of 50, 20, and 0 mg/d, predictably finding that opiate-positive urines increased as dose decreased (26). None of the studies explored doses exceeding the 100 mg/d barrier, even though opioid addicts who are not receiving adequate doses of methadone might be expected to respond poorly to treatment, just as would any patients prescribed deficient pharmacotherapy for any other chronic medical condition (20).

Strain et al. (27) recently reported a trial enrolling 192 MMT patients randomized to receive daily methadone in a defined "moderate" dose range of 40–50 mg/d or a "high" dose of 80–100 mg/d. Over the course of 30 weeks, the "high-dose" group had statistically significant lower rates of opioid-positive urines than the "moderate-dose" group (53% vs. 61.9% respectively, $p = 0.047$). However, this difference in illicit opioid use outcomes between the two dosage levels, with an absolute risk reduction of only 8.9%, was remarkably modest.

In this study (27), both the "moderate" dose (mean 45.8 mg/d) and the "high" dose (mean 89.5 mg/d) were clearly subtherapeutic for many patients. The authors conceded that "it is possible that dosages in excess of 100 mg/d may be required for optimal benefit in some patients."

As a further example, Magura et al. prospectively followed for up to three years in treatment more than 1000 patients newly admitted to New York City MMT clinics (28). Three groups were identified in terms of dosing levels established within the first 3 months: 42% were at "low dosage" (mean = 34 mg/d); 39.4% received "medium dose" (mean = 58 mg/d); 18.4% were considered "high dose" (mean = 84 mg/d). Neither health status and concurrent use of prescribed medications nor SMLs were assessed.

This investigation found no association between methadone dose level and continued heroin abuse. The authors noted that continued heroin use resulted in patients receiving increased methadone doses, although they acknowledged that "it may be that such upward dosage adjustments [were] simply not high enough to achieve their aim." Indeed, the average methadone dose level for the entire sample population was 52 mg/d (±20 SD) with only 3% of patients averaging 90 mg/d or higher.

To explore the question of just what might constitute more appropriately "high" methadone dosing, Maxwell and Shinderman (9) identified a group of 164 patients who, despite methadone doses of up to 100 mg/d, had high rates (87%) of continuing illicit opioid use. These patients, assigned to a "high dose" (HD) condition, received clinically guided dose increases, resulting in a mean dose of 211 mg/d (range 120 – 780 mg). This cohort was compared to a randomly selected control group receiving an average dose of 69 mg/d (range 10 – 100 mg), drawn from a clinic population of 1100 patients.

Group characteristics differed in two significant ways. Prescription psychotropic medications were being taken by 63% of the HD group compared to only 28% of the control patients ($p < 0.001$). Also, the HD group reported taking larger amounts of daily heroin, spending more money on their addictions, than control subjects prior to entering treatment (mean $153/day vs. $87/day; $p < 0.001$).

The fraction of opioid-positive urine samples decreased from 87% to 3% in the HD group compared to a decrease from 55% to 36% in the control group. Furthermore, the one year or more retention-in-treatment rate for the HD group was 86%, compared to 35% for the general clinic population, a 51% absolute risk difference in favor or higher doses.

SMLs were performed on most of the HD group patients; when the trough levels were less than 200 ng/mL, patients exhibited objective signs of abstinence syndrome. As methadone dose was increased and the SML rose, objective signs disappeared, but some patients still reported subjective symptoms of withdrawal. This is consistent with a report by Loimer and Schmid (4) which calculated that even patients with trough plasma levels exceeding 600 ng/mL may complain of withdrawal symptoms. Further increases in methadone dose, reaching a therapeutic SML range, alleviated all symptoms and continued heroin abuse abated (see Table 1).

Maxwell and Shinderman noted (9) that SMLs were somewhat helpful in confirming inadequate methadone dose, but were not useful for determining optimal dose. "Although 400 ng/mL is the lowest SML that is usually considered effective in alleviating objective signs and subjective symptoms of [abstinence syndrome]," they wrote, "some HD group patients had SMLs of 800 – 1200 ng/mL when titrated to doses resulting in no signs of opioid [overmedication], no symptoms of withdrawal, and no illicit substance use."

The higher-than-expected SMLs necessary for optimal dose in the HD group might have been predicted from their larger heroin habits prior to MMT and their greater intake of prescription psychotropic medicines, some of which might have interacted to accelerate methadone metabolism overall or to selectively reduce levels of the active R-enantiomer. Testing for serum R/S-enantiomers would have been enlightening, but this test is not yet available in most laboratories. In lieu of this, Maxwell and Shinderman proposed that (9) "medical evaluation of objective signs and subjective symptoms is a sensitive, reliable, and cost-effective method of dose titration." Furthermore, this study concludes that (provided the clinical picture does not suggest opioid overmedication) there does not appear to be a maximum limit for optimal methadone dose.

Treating Patients, Not Test Results

There is no way of prescribing a single best methadone dose to achieve a specific blood level as a "gold standard" for all patients. In clinical practice, when faced with continued illicit drug use or patient-reported withdrawal or craving complaints, serum levels may confirm what is happening to methadone in the patient's system. SMLs can be an educational aid for encouraging a fearful patient to accept a more adequate methadone dose or for assuring a less experienced colleague, a wary relative, a reluctant insurance company, or a circumspect regulatory agency, that a dose increase is justified.

Since SML results are not reliable for determining optimal dose, clinical symptoms and signs become particularly important as a dosing guide, as this final example illustrates:

> A 33-year-old woman was initially titrated to a methadone dose of 100 mg/d (trough SML 680 ng/mL), but she continued heroin use. After 6 weeks at that dose and ongoing psychotherapy in the MMT program, her heroin use continued and a repeat trough SML was performed. At

> the time of phlebotomy, the patient was diaphoretic, restless, yawning, pupils 7 mm, and complaining of severe drug cravings — the SML was 810 ng/mL. Her dose was titrated upward to 400 mg/d, at which time she reported abstinence from illicit opioids and relief from cravings, with no clinical signs of opioid overmedication. After 5 months of continued opioid abstinence and patient-reported feeling [of] "normal" at this dose, her trough SML measured 1800 ng/mL; peak SML was 3400 ng/mL. The patient has been successfully maintained on 400 mg/d of methadone with continued illicit drug abstinence for more than three years.

In this case, the final peak/trough ratio of 1.9 (3400/1800) was within a desirable range (1), although the SMLs might seem excessive. Given the inter-individual variances of methadone metabolism observed by Eap et al. ([13] described above), only a fraction of this woman's serum methadone might have been the active R-methadone enantiomer; however, enantioselective testing was unavailable to establish this. Although this case may seem a rare example, it strongly demonstrates the importance of being guided by clinical signs and symptoms in dosing decisions. The first SML reading of 680 ng/mL mistakenly suggested the patient was getting "enough" methadone, but a 400 mg/d methadone dose and very much higher SML proved necessary to achieve optimal therapy.

Dole has stressed (3), even when the means for repeated measurements of SMLs are available, that any rigid set of dosing guidelines would be misleading. "Fortunately, this laboratory support is not needed," he wrote. "An experienced clinician can judge the adequacy of the dose from [the] effects." He advised, as did Maxwell and Shinderman, that adequate methadone dosing can be readily identified by listening to patient-reported symptoms, considering their timing in relation to daily dose, noting the patient's response to a change in dose, and evaluating his or her emotional stability.

Dole believed (3) that "the patient's clinical state is correlated reliably with the blood level and the degree of tolerance." Similarly, Hiltunen and colleagues found (10) that patient-reported subjective withdrawal symptoms correlated significantly with SMLs, and that patients may still experience and complain of such symptoms in the absence of any objective signs.

Dole's classic advice of "listen to the patient" seems all the more apropos in view of recent discoveries about the individual differences in methadone metabolism discussed above. However, pharmacokinetics do not explain everything, and there may be interacting pharmacodynamic host factors, such as the potential role of psychosocial influences (15). In addition, new research suggests genetic variations at the opioid or the dopamine receptors in the brain (29).

Finally, environmental factors also need consideration, as the drug scene has greatly changed. Over the years, street heroin has become purer in quality and lower in price, making it more economically accessible. A report of the U.S. Drug Enforcement Agency noted that from 1980 to 1995, the price of a milligram of street heroin decreased from $3.90 to $1.04, while its purity increased from 3.6% to 39.7% (30). Purity levels exceeded 60% in New York, Philadelphia, and Newark (31).

Higher-purity street heroin has led to its increased use, since it can be smoked, snorted, or otherwise inhaled without the need for hypodermic injection. This has attracted many new users among young, working, white, and middle-class populations (31). Those who snort or smoke heroin increased from 55% of users in 1994 to 82% in 1996 (32). All of this suggests that today's increasing numbers of opioid addicts often have more refractory drug dependencies, which will require higher doses of methadone during MMT.

There have been cases of patients requiring in excess of 2000 mg of daily methadone, possibly due to the metabolic interactions with other medications or organ dysfunction. However, in this era of HIV/AIDS, hepatitis C, tuberculosis, and other widespread infectious diseases among substance-abusing populations, the "exceptional" MMT patient requiring exceptionally high doses may become more of a "rule" than presently imagined.

Conclusion

There is no scientific rationale for maintaining patients at lower than optimal methadone doses, yet some MMT practitioners and researchers seem philosophically committed to dosing regimens that expose countless patients to unnecessary abstinence syndrome and illicit opioid use each day. Dole (3) has written "the results are generally poor, [since] limiting or withholding medication that reduces drug hunger increases the need for illicit narcotics."

Therapeutic drug monitoring tests can play a useful role in MMT programs. However, a basic precept of sound medical practice is to trust clinical findings — withdrawal signs/symptoms, drug craving, and continuing opioid abuse — as indicators of inadequate versus adequate dose. Each patient presents a unique clinical challenge. Practitioners are cautioned against making the mistake of "treating test results" or dogmatically adhering to biased preconceptions of what is "enough" methadone, and thereby ignoring patients' needs for optimal methadone doses.

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Treatment of Pain in Methadone-Maintained Patients

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Abstract

Patients with opioid dependency experience trauma, acute medical illness and chronic diseases, and may have to undergo surgery to the same extent as other individuals. They need to be treated for relief of symptoms, including pain. Undertreatment or inadequate treatment of pain for these individuals is a particular problem because of opioid dependency and/or methadone maintenance treatment. The guiding principles governing treatment of these patients are to maintain the methadone treatment and to use short-acting narcotics administered at higher doses, and to do so as often as necessary, preferably on a fixed schedule, to relieve the pain. Supplemental analgesic medication may also be employed, except that opiate antagonists must be avoided.

Key Words: Tolerance, methadone, analgesic, methadone maintenance, pain, pain treatment, opiate, opioid, heroin, analgesia.

Introduction

OPIOID AGONIST THERAPY is an accepted medical treatment for opioid addiction, with documented efficacy. Methadone maintenance treatment of addiction (MMT), the most common form of opioid agonist therapy, is approved by all major medical and professional organizations concerned with addiction treatment. Approximately 179,000 persons (1) in the United States are currently enrolled in methadone treatment. The federal government advocates expanded availability of the modality. Although some individuals require opioid treatment of addiction on a time-limited basis, others require treatment on a long-term basis and may, during the course of treatment, present with medical disorders associated with acute or chronic pain. Although the problem of pain management during methadone maintenance has received little systematic attention, pain is a common problem in this population and likely to become more so as the population ages and a larger number of medically ill patients are enrolled in programs.

Undertreatment of pain, which is a recognized problem in all populations, occurs with relatively greater frequency in those with histories of chemical dependency, including patients enrolled in MMT (2). The barriers to effective pain treatment are multiple and complex. Its undertreatment may be related to deficiencies in clinician practice, including the failure to assess pain and co-morbid disorders adequately, and to inadequacies in their knowledge and skills. Additionally, persistent pain may be ascribed to patient-related problems, such as under-reporting of pain, or to systems-related problems, such as

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inadequate insurance or reimbursement for analgesic therapies.

In populations with chemical dependency, analgesic therapy using opioid drugs requires a high level of knowledge and skill on the part of responsible clinicians. In the case of methadone-maintained patients, effective analgesic therapy requires careful attention to both clinical and pharmacologic principles. Misinformation about the pharmacology of opioids, including methadone, may contribute to inadequate pain management. Misinformation about opioid tolerance is also common. Physicians may also believe erroneously that methadone taken for maintenance is sufficient to provide adequate analgesia. In addition, there are widespread concerns regarding possible legal sanctions related to physicians' use of state-mandated prescription forms for opioids.

When an MMT patient is in pain, aberrant drug-related behaviors may occur, and may raise concerns about relapse. A detailed assessment often indicates that desperation arising from the unrelieved pain is more likely to be the cause. In the context of a medical problem such as pain, simple labeling of aberrant behaviors as abusive "drug seeking" is inappropriate. Without a careful assessment by a concerned and knowledgeable clinician, behaviors can be misinterpreted.

Cycles of clinician concern and patient distress may be difficult to interrupt. The process requires the ability to perform a sophisticated assessment of both pain and drug use, and the ability to respond to unrelieved pain with appropriate interventions. Professionals working with addicted individuals need to become aware of their own possible biases, which may detract from their care of these patients. Examples of common biases include (3):

> "They are morally culpable for their addiction. It's their fault."
> "Pain is 'payback' for their own vices and for getting high."
> "They are deceitful and always manipulating to get drugs to get high."

All of these issues can become particularly daunting when the pain and clinical context suggest a role for long-term opioid analgesic therapy in patients receiving methadone maintenance. To address these issues, this article briefly reviews the principles of opioid agonist therapy of addiction and the principles of pain management for methadone-maintained patients.

Methadone as a Therapeutic Agent

Pharmacologic Aspects of Methadone

Basic Pharmacology

Methadone is a synthetic opioid with a long and variable half-life (between 12 and 100 hours (4). Although it can be administered intravenously or intramuscularly to treat pain, its utility as a maintenance medication in the treatment of opioid addiction is based on its long half-life and ready, reliable absorption when used as an oral medication. The slow onset of methadone taken orally does not produce a sudden "rush," and produces no euphoric effects in most patients (5). As a treatment for opioid addiction, it is effective in blocking craving and withdrawal for 24–36 hours.

For decades, methadone has also been used as an analgesic, and interest in the drug as a treatment for pain has been increasing because of recent evidence that the commercially available racemic mixture includes an isomer that does not bind to opioid receptors, but is an antagonist at the n-methyl-D-aspartate (NMDA) receptor. By blocking this receptor, this d-isomer could potentially yield analgesia by a mechanism that potentiates that produced by binding of the l-isomer to the opioid receptor. Moreover, NMDA-receptor antagonism reverses opioid tolerance, and this effect may explain the unexpectedly high analgesic potency of methadone when it is administered to patients who are receiving another mu agonist drug.

The analgesic effects of methadone typically last 4–8 hours after a dose. Although some patients are able to achieve stable analgesia with dosing every 12 hours, most patients require analgesic doses every 6–8 hours, and some can avoid end-of-dose failure only by dosing every 4 hours.

Single-dose, controlled analgesic studies indicate that methadone is slightly more potent, on a milligram per milligram basis, than morphine sulfate (6). These studies have limited relevance to chronic administration, during which the combination of kinetic factors (a slow and gradual increase of plasma concentration because of the long half-life) and dynamic factors (increased potency presumably because of the NMDA-receptor antagonism of the d-isomer) produce an unexpectedly high potency, gradual accrual of effects over days to a week or more, and variability in response based on the existing therapy. As a result of these factors, current guidelines indicate that the use of methadone for pain should be initiated at a dose that is 75–90% lower than the calculated equianalgesic dose. This initial dose is usually co-administered with a short-acting opioid "rescue" medication. Close monitoring during dose titration is needed until sufficient time has passed at a stable dosing level to ensure that the plasma concentration has plateaued. This steady-state plateau, which requires 4–5 half-lives to achieve, can in the case of methadone require days to weeks.

Tolerance

Tolerance is the loss of drug effect over time, induced by persistent exposure to the drug (7). Alternatively, tolerance can be defined as the need to increase the dose to maintain the initial effects of the drug. Tolerance may develop to any opioid effect, and tolerance to different effects typically occurs at varied rates (8, 9). Tolerance to some adverse effects of a drug, such as respiratory depression and nausea, is clinically favorable and typically occurs within days to weeks. Tolerance to the respiratory depressant effects allows stepwise dose escalation to occur in a manner that is safe and can optimize analgesic outcomes (9). As a consequence of this phenomenon, some patients can be gradually titrated to very high doses of methadone — equivalent to many grams of morphine per day — in an effort to attain pain relief.

In contrast to tolerance to adverse effects, analgesic tolerance can be a clinical problem. Fortunately, however, extensive clinical experience has documented that the doses required to maintain analgesia typically stabilize in the absence of progressive disease. Although dose escalation may be needed periodically to sustain analgesia, tolerance is seldom a problem in the clinical setting. The corollary to this observation is equally relevant: when a need to increase the dose does materialize, the clinician should search for worsening disease, rather than assume that analgesic tolerance has occurred.

Physical Dependence

Physical dependence is an expected form of physiologic adaptation which occurs as a result of regular drug exposure and is reflected in the development of an abstinence, or withdrawal, syndrome when there is abrupt cessation of the drug, administration of an antagonist, or rapid decrease in dose (10). Physical dependence is not addiction, and much of the misunderstanding about the risk of addiction occurs because these terms are often mistakenly used as synonyms. Although physical dependence must be assumed to exist after a few days of opioid administration, it is, like the phenomenon of tolerance, neither necessary nor sufficient to yield an addictive disorder. Physical dependence that occurs in the course of therapeutic opioid use does not indicate addiction and should never be labeled in this manner.

Addiction and Drug Craving

Opioid addiction is a neurobiologically based disorder, with social and psychologic influences, characterized by a pattern of maladaptive behaviors, including: loss of control over use, craving and unwarranted preoccupation with non-therapeutic use due to craving, and continued use of the drug despite harm resulting from use. Physical dependency and tolerance may or may not be present in addiction.

Opioid addiction occurs as a result of neurobiologic changes within the limbic reward systems, changes that are induced in biologically vulnerable individuals through repeated use of rewarding drugs. The induced neurobiologic changes are protracted and appear to drive persistent drug craving. Addiction is associated with down-regulation of the hypothalamus-pituitary adrenal axis (11). Drugs with rapid onset of action are believed to pose the greatest risk for development of addiction in vulnerable individuals (11).

Treatment of Opioid Addiction with Methadone

Rationale

Opioid agonist therapy of addiction is based on the understanding that stable and continuous occupation of opioid receptors in the limbic system and other brain centers associated with addiction blocks opioid craving without causing euphoria or significant cognitive changes or sedation. This permits the user to focus on life activities unrelated to obtaining and using drugs, resulting in gradual return to normal function and a productive lifestyle.

Methadone has a relatively slow onset of action and a long half-life. With daily use of consistent doses, relatively stable blood levels of the drug are achieved. Methadone causes less stimulation of limbic reward centers than shorter-acting opioids, has a relatively low abuse potential, and, at relatively high stable blood levels, it blocks the "high" obtained from use of short-acting opioids. These attributes make methadone particularly effective as therapeutic opioid agonist agent. Recently, other agents, including buprenorphine and levomethadyl acetate (LAAM), have been introduced as therapeutic agents. They appear to have good safety and efficacy profiles as therapeutic opioid agents in addiction treatment, and it is likely that their use in clinical practice will increase over time.

Documented Benefits

Methadone maintenance treatment for addiction normalizes the impairments associated with opioid addiction (2, 11). Methadone treatment has been documented to reduce the use of illicit opioids and to reduce morbidity and mortality among heroin addicts. Patients stabilized on methadone are able to take advantage of educational, vocational and employment opportunities. Increases in social stability and productive behavior have been documented in numerous studies over the past three decades (12). Outcomes of MMT for addiction are improved when combined with counseling, social support, and educational or vocational opportunities (12).

Methadone Maintenance for Hospitalized Patients

Under federal law, methadone may be prescribed for maintenance therapy of addiction in ambulatory patients only by physicians who have a special license to prescribe opioid therapy of addiction and who are affiliated with a licensed opioid treatment program. However, any physician with a standard, unrestricted Drug Enforcement Administration (DEA) license may prescribe maintenance methadone to a patient who is hospitalized for a cause unrelated to addiction. That is, if a patient is admitted for an acute medical illness such as pancreatitis or renal lithiasis, or for a surgical procedure, any treating physician may, and should, prescribe for the patient's maintenance methadone while the patient is hospitalized. It is imperative that maintenance methadone be continued during hospitalization in order to avoid withdrawal and potential complications in medical, surgical and pain treatment. The guiding principles for prescribing medications to MMT patients include:

- Avoid medications with antagonistic properties, such as naltrexone and agonist/antagonist opioids such as pentazocine

- Morphine or other opioids should be administered to control pain. The dosage may have to be increased because of tolerance induced by methadone.

- A fixed schedule of administration is preferable to a variable schedule.

Clinical Use of Methadone as an Analgesic Agent

Methadone has been used as an effective analgesic agent for decades. New information about NMDA receptor antagonist actions, combined with its relatively low cost, has generated increasing interest for use in pain management. The use of methadone as a treatment for addiction has complicated efforts to appropriately position the drug for analgesic therapy. For example, some physicians erroneously believe that a special license is required to prescribe methadone as an analgesic agent. This concern is particularly strong when the patient is receiving MMT and the use of methadone is being considered for pain. Physicians must be reassured that a specialized license to provide opioid therapy is required only when methadone is administered for the treatment of addiction, even if the patient is also receiving the drug as part of MMT. Methadone may be prescribed for the treatment of pain in any patient, including a patient on methadone maintenance therapy of addiction, without a specialized license other than a standard DEA license. Careful documentation is required if methadone is selected as an analgesic, especially in MMT patients.

Because of methadone's use on a once-a-day basis for the treatment of addiction, many physicians assume that methadone can be used once daily for pain. A very large clinical experience refutes this. Most patients will require a dose interval of 6 – 8 hours to maintain analgesic effects.

Although it is most often used orally both for maintenance therapy and as an analgesic, methadone may be used parenterally when the oral route is unavailable. Although methadone may be too irritating for continuous subcutaneous infusion, it can be administered by parenteral bolus injection or infusion, like any other opioid administered for pain.

Finally, some physicians believe that methadone has a unique profile of analgesic actions and side effects, although this has not been clearly documented from studies of long-term therapy for pain. There is very large intra-individual variability in the response to opioids, and a single patient may experience different patterns of analgesic responses and side effects to each of the pure mu agonist opioids. When methadone and other drugs are compared at equianalgesic doses, there is no evidence for systematic differences between them; however, an individual patient may or may not find a switch to methadone to be a favorable intervention.

Principles of Pain Management in MMT Patients

Common Problems in the Management of Pain in Patients on MMT

Patients receiving MMT for addiction often receive sub-optimal, or even negligible, treatment of acute pain while hospitalized. A series of approximately one hundred reports indicates the following common errors in management:

- Methadone doses were lowered in the hospital, and as a result, patients experienced withdrawal symptoms.
- Pain medication was denied because the clinician believed that the patient's chronic maintenance methadone doses would provide adequate analgesia.
- Patients for whom analgesics were prescribed were usually inadequately dosed because clinicians feared that medication in addition to the patient's prescribed methadone would cause respiratory depression.
- Patients were told to withdraw from methadone prior to surgery or other procedures because of the incorrect belief that methadone may interfere with the procedures and/or impair their general health.
- During hospitalization, patients' maintenance dose was increased in an attempt to achieve analgesia. Patients were then released from the hospital on excessively high doses of methadone.
- Patients reported that opioid antagonists were inappropriately administered, inducing severe withdrawal.
- Because of the stigma associated with MMT, many methadone patients had negative experiences with health professionals when their status as patients became known (12, 13). As a result, some methadone patients admitted to an emergency room or a hospital concealed their status from staff, with occasional dire consequences (e.g., administration of pentazocine or other agonist/antagonist drugs, which can precipitate sudden withdrawal) (14).

Clinical Issues Affecting Pain Management in MMT Patients

Role of Opioid Therapy in Pain Treatment

There is widespread consensus that opioid therapy is the mainstay approach for the treatment of moderate-to-severe acute pain, and moderate-to-severe chronic pain associated with cancer or AIDS. As noted previously, undertreatment is common despite this consensus, and chemically dependent patients are more likely to be undertreated than those without this history. Although a history of addiction and MMT for addiction may yield challenges during opioid therapy for pain, there is clinical agreement that opioid drugs should still be considered the major approach in these settings.

The role of long-term opioid therapy for noncancer-related pain is evolving rapidly. There are now consensus statements from major professional societies, including the American Society of Addiction Medicine, that acknowledge the appropriateness of this treatment for selected patients. Although the use of this therapy for those with a history of chemical dependency has barely been studied, it is clear from a clinical perspective that, when opioids are required to relieve significant and persistent chronic pain in this population, they must be utilized with appropriate care and structure to avoid complications of use.

Careful assessment must be done when opioid therapy of chronic pain is contemplated for individuals with addictions, in order to clarify the state of the addictive disorder (active, at risk or recovering); to determine the presence or absence of co-morbid psychopathology; to assess the degree to which unrelieved pain may be driving aberrant drug-related behaviors; and to establish a means to structure treatment in a way that would reduce the risk of inappropriate use. The active abuser may be very different from the patient in MMT or in stable drug-free recovery, and the decision to consider long-term opioid therapy for chronic pain in these patients presumably carries very different degrees of risk.

When deciding whether to consider long-term opioid therapy for chronic pain in patients with a history of chemical dependency, the clinician should also recognize the difficulties that the patient may experience because of anxiety about relapse, abandonment by friends, or challenges from addiction treatment programs. In all cases, the treatment requires a detailed assessment, including an open discussion with the patient, concerning all risks and benefits.

Anxiety Regarding Treatment

Many patients who are receiving MMT for addiction recognize that pain is often inappropriately managed in patients on MMT, and this may cause significant anxiety among those confronting injury, illness or surgery. Patients often fear ineffectively treated pain, loss of effective maintenance therapy, and the emergence of acute withdrawal, as well as the possibility of disrespectful treatment by health-care personnel. Anxiety related to these fears may in turn result in behaviors that become challenging to clinicians. Reassuring the patient that pain management is a high priority, including the patient in decision making, and adhering to good basic principles of pain management are critical to providing effective pain treatment.

MMT patients may also experience anxiety about using opioid medications for pain. Some believe they should "grin and bear" their pain because of concern that taking an opioid analgesic constitutes a relapse and will lead to re-addiction (15). These patients and their families and physicians often need reassurance and encouragement to accept the analgesic treatment. It is sometimes helpful to point out that medications prescribed for acute pain are most often time limited and that relief of pain is essential for a quick and healthy recovery.

Many former illicit drug users fear losing control over medications and thus refuse any analgesia. Methadone patients receiving a blockade dose can be reassured that their daily dose of methadone will generally block any euphoric effects of the analgesic medications and that analgesics will only produce relief of pain. Methadone patients on lower doses can similarly be advised of a partial blockade and assured that in all probability they will feel very little euphoria, if any at all, from pain medication. If patients persist in declining medication, their request for no pain medication should be respected and non-medication approaches to pain control implemented whenever possible. However, in some patients, pain may eventually overcome this fear, and a request for pain medication may be made.

Some methadone patients fear that use of analgesic opioids will result in the need to increase their maintenance dose of methadone. It has been documented, however, that use of opioids for analgesia does not result in increased dose requirement for maintenance therapy once acute pain is resolved (16). With treatment, methadone patients will most likely continue with their usual maintenance treatment.

Adequacy of MMT

In order for pain management to be effective, patients who require maintenance therapy of addiction must be on an effective dose of methadone for their addiction treatment. Patients receiving subtherapeutic doses, who are experiencing early symptoms of withdrawal or craving, will be much more difficult, or impossible, to treat for pain. It may be difficult for patients on subtherapeutic doses to distinguish between the pain from surgical procedures and the pain from withdrawal syndrome. Opioid blockade may reduce the risk of euphorigenic effects and provide relative protection against re-addiction and relapse associated with the therapeutic use of an opioid analgesic.

Pain Sensitivity and Analgesic Responsiveness in MMT Patients

Although supporting data are inconclusive, there is suggestive evidence that methadone-maintained patients may be more sensitive to noxious stimuli — i.e., experience a relatively high level of pain following a noxious event — than non-maintained individuals. A study by Compton et al. (17), which examined pain, pain thresholds and pain tolerance in the presence of experimentally induced cold-pressor pain in humans, demonstrated that stable doses of methadone used as maintenance therapy appear to provide no analgesic effect and that methadone maintenance patients overall have lowered pain thresholds (increased pain sensitivity) and less pain tolerance than non-maintained individuals.

This research affirms that the usual dose of methadone used chronically for opioid therapy of addiction does not relieve pain and that individuals receiving MMT for addiction may require more aggressive pain management because of a predisposition to pain. If opioid analgesia is selected for the MMT patient, relatively high doses may be needed, both to overcome whatever level of analgesic tolerance the MMT has produced and to address the predisposition to pain (17).

Co-morbid Psychiatric Disorders

Studies suggest that 30–80% of substance abusers suffer from co-existing psychiatric illness (14). Anxiety, panic disorder, and the range of mood disorders (depressive and bipolar) which have a high prevalence in the addiction population may all be associated with bodily discomfort, pain itself, or distorted somatic perception (14). Psychiatric evaluation and effective treatment can be crucial to relieving the pain syndromes in many of these people.

Structure of Pain Therapy in Methadone-Maintained Patients

Discussion and Documentation of Benefits, Risks and Structure of Therapy

Unless there is compelling evidence suggesting otherwise, all patients presenting with complaints of pain, including those with addictive disorders, should be evaluated and treated for their presenting pain complaint. Most often, individuals seeking opioids for non-medical uses will declare themselves eventually, through a pattern of aberrant behaviors.

If opioid therapy is selected as an intervention for pain in the patient with addictive disease, it is important to establish a clear understanding with the patient. Appropriate discussion and documentation of the potential risks and benefits of therapy, as well as the structural guidelines of treatment, should be made. If therapy takes place in the ambulatory setting and is expected to continue for a prolonged period of time, it may be helpful to detail this understanding in the medical record and have it signed by both treatment provider and patient. This is often referred to as a "contract," agreement, or covenant (18). A number of structural supports may facilitate effective pain therapy in patients with addictive disorders and should be noted in any agreement between patient and provider. These are discussed below.

Single Prescriber

In the ambulatory setting, it is best for the patient to have one physician prescribe all the analgesics and, preferably, all controlled medications. This provides continuity of care, eliminates overlap of medications, reduces the risk of drug interactions, and is reassuring to both the patient and the clinicians. In this arrangement, the physician prescribing analgesic medications should inform other doctors who are prescribing for the patient, including the methadone prescriber, primary care physicians and any consultants who see the patient on a regular basis.

Team Approach

For those patients in MMT for addiction, it is essential that their team of counselors, nurses and others participate in the evaluation and treatment-planning process. The treatment staff must know what medications the patient is prescribed in order to observe for effects and side effects, be aware of potential drug interactions, and support the individual in his or her recovery.

Some MMT patients who are receiving opioids for chronic pain choose to drop out of their formal MMT program. Although using the opioid for pain may continue to block craving, the physician prescribing the drug for pain must carefully document that the intention of therapy is analgesic and not addiction management. A decision to leave the MMT program should be carefully discussed with the patient and members of the treatment team. It may be convenient, but such a decision may eliminate an important source of support for the patient.

Appropriate Controls on Medication Dispensing

When possible, it is best for the patient to obtain all prescriptions from one pharmacy. This facilitates tracking of medications. The patient should be asked to consent to ongoing contacts between the prescriber and the pharmacist. When a patient has difficulty controlling the use of medications, he or she should be given medications in small quantities, at frequent intervals. Some patients require daily dispensing from their pharmacy. This is often impractical, and sometimes a trusted other may dispense medications to a patient.

Documenting Use of Medications

It is often helpful to ask patients to bring their medications to each clinic visit so that care providers can observe whether the patient is using medications as prescribed. If concerns arise regarding whether or not a patient is using the prescribed medications, urine screens may be helpful for documentation. However, the clinician must be aware of the usual ranges that the particular laboratory utilizes when specific tests are requested, and what the reporting cutoff limits are for particular drugs; there is great variability among laboratories.

In rare instances, if a patient appears highly tolerant to medications and requires very high doses, use of the medication can be confirmed by asking the patient to take the prescribed dose while under observation. An opioid antagonist should be available in case the patient has been diverting medications and demonstrates no tolerance to the sedative or respiratory effects of the opioid. In patients on blocking doses of opioids, such side effects are not expected, but caution is appropriate nonetheless.

Managing Reported Losses

On occasion, clinicians who are prescribing long-term opioid therapy to a patient with a history of chemical dependency are asked to replace a prescription that is reported as lost or stolen. From the start, there should be a clear agreement about how such circumstances will be managed, and this should be documented in the agreement. It is helpful to advise patients that they are responsible for keeping the prescriptions and medications safe. One way to handle the problem of lost or stolen medication is to request that all losses or thefts be reported to the police. The police report will have to be presented and placed in the patient's record before any replacement medication can be prescribed. Some clinicians follow a practice of replacing only a single reported loss or theft and advising the patient that he or she will have to accommodate to any subsequent loss or, if the occurrence is frequent, therapy may be discontinued.

Clinical Principles of Pain Treatment for the Methadone-Maintained Patient

Continuation of Maintenance Methadone at Unchanged Dose

A patient on MMT who presents with pain should be continued on his or her usual dose of methadone for maintenance. This should usually be given orally in one daily dose. However, if the dose cannot be verified, it is safest to give the reported daily dose in three to four divided doses at appropriate intervals and observe the patient's response, to assure that a potentially dangerous dose is not given. If the daily dose cannot be confirmed and if the oral route is unavailable, one-half the usual daily oral, in divided doses, should be given parenterally. Continuing treatment thereafter should be based on the patient's response.

Measurement of Pain

Opioid analgesics should be titrated according to reported pain, as with all patients reporting pain. Use of pain scales such as a numeric pain scale (0 – 10) or a visual analogue is recommended in order to evaluate both pain and responses to pain treatment. Because of relative tolerance to opioids and possibly lowered pain thresholds, MMT patients often will require higher-than-standard analgesic doses given at more frequent intervals. This must be established with clinical observations (17).

Choice of Opioids to Provide Analgesia

Although methadone is an effective analgesic, it is generally preferred to select an alternative mu agonist opioid such as morphine, hydromorphone or oxycodone, to provide analgesia in methadone-maintained patients. This allows clear distinction between treatment of addiction and treatment of pain, and lessens possible confusion over clinical issues of pain and addiction. In addition, because of its relatively slow onset of action and long half-life, methadone may be difficult to titrate rapidly enough to meet acute pain needs.

In some cases, however, methadone will be the preferred analgesic (this usually relates to cost). If the patients remains in MMT, the treatment must include visits to the MMT program to receive a single daily dose for addiction, and visits to the physician who treats the pain, for a prescription that will be filled by a regular pharmacy; the latter will provide analgesic methadone, to be administered several times per day on a fixed schedule. This approach is not pharmacologically necessary, of course, but is required by regulation if the methadone is still being used to treat the addiction. There are anecdotal reports of former MMT patients who receive prescriptions for analgesic methadone.

Long-acting opioids, such as controlled-release oral morphine, oxycodone, or hydromorphone (soon to become commercially available) or controlled-release transdermal fentanyl, provide consistent pain relief for continuous pain, while short-acting opioids are more rapidly effective for addressing intermittent, incident or breakthrough pain.

Titration and Scheduling of Analgesic Medications

A fixed schedule is preferable to a variable "prn" schedule. For an inpatient, this avoids the request for opioids, which may be interpreted by some staff as pathologic drug-seeking behavior, rather than the seeking of pain relief. For ambulatory patients, it avoids the situation where the individual with an addictive disorder has to make a decision as to whether or not to take a potentially rewarding or reinforcing drug based on subjective pain level, a situation which may cause confusion, distress or, possibly, an escalating pattern of pain and medication use.

If only intermittent analgesia on an irregular basis is required, it is helpful, when possible, to link doses with activity or time, rather than increased pain alone, in order to avoid the potentially reinforcing effects of opioids on pain perception. In the case of the ambulatory MMT patient requiring additional opioids for analgesia, therefore, treatment may consist of a single methadone dose per day as addiction therapy, plus a fixed schedule of the opioid as used for pain.

It is important to be aware that individuals on methadone maintenance therapy of addiction and those using opioids chronically for analgesic purposes will often require relatively high doses of opioids at relatively short intervals, due to tolerance. Opioids should be titrated to reported effect while observing for improvement in pain and function versus signs of overuse, abuse or addiction. Ambulatory patients should be given medications in quantities that both they and their providers are confident that they can control.

When planning long-term opioid therapy in the ambulatory setting, it is often useful to begin with a small prescription, such as a seven-day supply. Before increasing the dose independently, the patient should be given instructions to contact the prescribing physician if the medication is not effective. The frequency of future prescription refills should be determined by effective dose, adherence of the patient, and the nature of the illness.

Use of Patient-Controlled Analgesia

Patient-controlled analgesia (PCA) may be used with MMT patients who are believed to be in secure addiction recovery. A continuous background infusion may be used with the PCA component, if indicated. PCA allows patients to titrate their own analgesic needs without frequent medication requests to health-care staff. These requests, in an individual with addictive disease, are often perceived as drug-seeking behaviors. Doses should be titrated to effective reported analgesia, while observing for side effects such as intoxication or persistent sedation, which may occur with overuse. Caution is indicated if a patient is not securely in recovery, may be at risk for relapse, and/or has visitors who are actively abusing opioids, since PCA makes IV forms of opioid reasonably available to tamperers.

Avoid Agonist-Antagonist Drugs

A patient using methadone or other mu agonist opioids on a regular basis must avoid the use of opioids with agonist-antagonist properties, such as butorphanol (Stadol®), pentazocine (Talwin®), nalbuphine (Nubain®), and dezocine (Dalgan®). Such drugs provide analgesia through activity at non-mu opioid receptors, but act as antagonists at the mu receptor, thus reversing the actions of methadone or other therapeutic mu agonist opioids. Therefore, they may precipitate an acute withdrawal syndrome in patients using mu agonist medications such as methadone (16).

Avoid Meperidine and Propoxyphene

Because individuals on MMT may be relatively tolerant to the effects of opioids, thus requiring high-dose therapy, meperidine and propoxyphene should not be used when prolonged or high-dose analgesia is anticipated. Normeperidine, a metabolite of meperidine, and norpropoxyphene, are potentially neurotoxic agents that may accumulate in such circumstances, causing tremors, agitation and even seizures in some cases. Meperidine is also very short acting, is poorly absorbed after oral administration, and provides only transient analgesia. It has few indications in the treatment of pain.

Non-opioid Approaches to Pain Treatment

Non-opioid pain treatment approaches may provide effective analgesia for patients with pain, in many settings, either alone or as a complement to opioid therapy. Non-opioid medications with analgesic activity include nonsteroidal anti-inflammatory drugs (NSAIDs), tricyclic antidepressants, anticonvulsants, corticosteroids, and local anesthetics, among others. Antidepressants and anticonvulsants may be especially helpful in treating neuropathic pain, which may be less responsive to opioids than is nociceptive pain. Non-opioid pharmacologic treatments should be dosed in the standard amounts used for analgesia in nonmethadone-maintained patients, since individuals on MMT are not expected to have tolerance to the effects or side effects of these medications. Only the opioid analgesic may need to be used in higher doses for the methadone patient, unless the patient has developed tolerance to non-opioid substances. For example, an MMT patient with concurrent alcoholism also may have developed tolerance to sedative-hypnotics. Another approach is that offered by anesthesiologists, such as nerve blocks and intraspinal infusion.

There are numerous non-medication approaches to pain treatment, beyond the scope of this paper, which may be helpful in individuals on MMT. These include psychological (e.g., cognitive, behavioral and other therapies) and physical modalities (e.g., physical therapy, analgesic modalities such as cold or heat, and neurostimulatory modalities such as transcutaneous electrical nerve stimulation, acupuncture and dorsal column stimulation). Attention to nutrition and weight (loss or gain) may also have a role in pain treatment.

Special Populations

Pregnancy

Treatment of the pregnant woman demands special physiologic considerations according to trimester, and attention given to the well-being of the fetus. It is generally agreed that the pregnant patient should receive as high a maintenance dose of methadone as is necessary to achieve blockade, so that she will cease using illicit opioid. The physiologic changes of pregnancy including slowed gastrointestinal absorption, expanded fluid load, and increased glomerular filtration, all indicate a possible need to increase the amount of methadone for maintenance, especially in the third trimester. As with other patients on MMT, it may be necessary to use higher analgesic doses of opioids to treat pain; opioids utilized to provide analgesia should be titrated to effect.

AIDS, HIV Infection and Cancer

The special needs of patients who have a history of illicit drug use and are infected with HIV are of critical relevance when considering pain management. It has been well documented that pain associated with HIV-related disease is routinely undertreated (2). The World Health Organization and U.S. Agency for Health Care Policy recommend that a cancer pain model of pain treatment be utilized in managing pain in patients with HIV-related illness. The complexity of the issues in treating these patients requires that the first step in their management be a comprehensive assessment. Careful attention to addiction recovery and to principles of pain management in MMT patients, as discussed above, is requisite to providing effective pain management for HIV-infected patients on MMT.

Care of Patients with Active Addiction

Patients with active drug addiction who present with acute or chronic pain due to injury, illness or surgery present special challenges to the pain treatment provider. It has been documented that periods of acute illness often represent opportunities for meaningful intervention in addictive disease, as patients are often confronted with their vulnerability to illness and, sometimes, specifically to the harmful sequelae of their disease. Attempts to engage the patient in addiction treatment should therefore be aggressive at these times. Clinicians not knowledgeable in addiction treatment should seek professional expertise when treating patients who are active drug users.

Pain management for all patients with addiction requires relatively tight controls, monitoring and documentation, while at the same time meeting the individual's analgesic needs through appropriate titration of medications and use of other modalities. A smooth course of analgesic therapy is often facilitated when addicted patients are reassured that the staff is aware of their addictive disorder and that every effort will be made to treat their pain; their addiction will not be an obstacle, if they are willing to work with the team. Opioid-addicted individuals should be assured that they will be given enough methadone to prevent withdrawal and craving while they are hospitalized. The relative tolerance to the analgesic effects of opioids in opioid abusers must be considered when titrating medications. The use of a written contract that is kept in the medical record, defining the regimen and explicitly stating the responsibilities of both the patient and the physician, may be especially helpful in treating these patients.

Summary

The methadone-maintained patient experiences as much pain in association with illness, injury, and surgery as do other individuals. Methadone used chronically for maintenance does not treat acute or chronic pain. Therefore, the methadone patient needs adequate analgesic medications prescribed to relieve pain.

Methadone-maintained patients who have pain often require relatively large doses of opioids at relatively short intervals to control their pain, since they have some level of tolerance to opioid medications. At a blockade dose of approximately 80–120 mg/day, the methadone-maintained patient has relatively high tolerance to the respiratory depressant effects of opioids, and will not experience drug craving or euphoric effects in association with short-acting opioids prescribed for relief of pain. Clinicians should therefore not feel apprehensive about the relatively large doses of analgesics often required to treat pain in methadone patients, but should observe patients carefully and adjust analgesic doses according to reported relief and observed effects. Methadone will not interfere with analgesic responses to opioids, although dose requirements may be higher than in non-maintained patients.

The simplest approach to the treatment of acute pain in the methadone patient is to prescribe adequate doses of an alternative mu opioid, while maintaining the maintenance dose of methadone. The type and dosing pattern of the opioid used should be determined with consideration of the type, intensity, and temporal pattern of the patient's pain.

When an opioid is used for chronic pain, successful therapy is predicated on a careful assessment of the pain, a detailed history of chemical dependency, and awareness of co-morbid physical and psychosocial factors. Treatment requires a knowledgeable and committed physician who will administer the opioid in doses required to attain analgesia, while monitoring the patient for other critical outcomes, including function, drug-related behaviors, and side effects. A team approach is often helpful.

Patients should generally not be withdrawn from opioid medications while they are experiencing acute pain. If it is necessary to change the maintenance dose of methadone for any reason, this should be done in consultation with the patient and the clinician who is treating the patient for his or her drug dependence. If basic principles of pain management are followed, analgesic management of the methadone patient should be as effective and safe as for any other patient treated for acute or chronic pain.

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HIV and HCV Infection among Injecting Drug Users

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Abstract

Background: Human immunodeficiency virus (HIV) and hepatitis C virus (HCV) are the two blood-borne pathogens most commonly transmitted among injection drug users via multi-person use of syringes and other injection equipment. However, important differences exist in the epidemiology of HIV and HCV within different populations of intravenous drug users.
Methods: A literature review was carried out to summarize publications describing the epidemiology and natural history of HIV and HCV in injection drug users.
Results: Among injection drug users worldwide, HIV prevalence varies from < 5% to > 80%, with annual HIV incidence between < 1% and 50%. More consistency is shown in HCV prevalence (50–90%) and incidence (10–30% per year). Host, environmental and viral factors that favor rapid spread of HCV among IDUs suggest that HCV infection in a population of injection drug users may become endemic over a relatively short period of time. Lower transmission efficiency for HIV also indicates that its spread among injection drug users may be somewhat slower.
Conclusions: Successful efforts to prevent transmission of blood-borne viruses among IDUs typically result in risk reduction; however, no intervention has resulted in elimination of risk behavior. To reduce HIV transmission, risk reduction may be sufficient, whereas control of HCV may necessitate the use of injection practices that guarantee elimination of exposure to equipment contaminated with even small amounts of blood.
Key Words: Substance abuse, injection drug use, HIV, HCV, epidemiology.

Before a person injects psychoactive drugs, a small quantity of blood is drawn into the syringe to determine if the needle has been properly located in the vein. Even if the person then injects "all" of the blood and drug mixture from the syringe, a small residue of blood always remains in the needle and syringe; this residue may not be visible to the naked eye. If a second person then uses this same needle and syringe for an injection, any residue in the syringe and needle may be transferred into the second user. Blood residue may also contaminate shared equipment used to prepare the drug for injection; the "cooker" used to heat and melt the drug into an injectable liquid and the "cotton" used to filter the drug as it is drawn into the syringe are two examples. There is substantial evidence that microtransfusions occurring when injecting with a contaminated syringe can transmit blood-borne pathogens among drug injectors (1, 2). Although there is less direct evidence that sharing of other equipment may spread infections, the data indicate that this is probably the case (3, 4).

Hepatitis C virus (HCV) and human immunodeficiency virus (HIV) are the two pathogens most commonly transmitted by drug users through the multi-person use ("sharing") of drug injection equipment (5, 6). These two pathogens are also likely to be responsible for the highest infectious disease morbidity and mortality rates among drug injectors worldwide. While both of these viruses can be transmitted through multi-person use of syringes and presumably via other drug injection equipment, there are important differences in the transmission dynamics of each virus within a population of injecting drug users (IDUs).

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Natural History and Epidemiology of HIV among IDUs

Persistent infection occurs in virtually all persons infected with HIV (7). The present data also indicate that, in the absence of effective treatment, the infection eventually results in an immunocompromised state which promotes opportunistic infections, certain malignancies and other fatal diseases (8–10). The length of time from initial infection to the development of severe immunodeficiency varies greatly among individuals (11). Epidemiologic studies have not shown that continuing to inject heroin or cocaine has any consistent effect on the rate of progression of HIV infection (12–15). However, it is conceivable that any actual effects of continued drug injection on disease progression are so modest as to be undetectable, and are statistically insignificant, even in large-scale epidemiological studies.

Over the last several years, there have been dramatic improvements in treatment of HIV infection. Highly active antiretroviral therapies (HAARTs) typically consist of three-drug combinations of antiretroviral agents, including reverse transcriptase inhibitors and protease inhibitors (16, 17). HAART can lead to suppression of viral replication and substantial increases in both the length and quality of life for HIV-infected persons (18–20). It is conceivable that by lowering HIV viral load in individual patients, HAART could also reduce the likelihood of HIV transmission to others in the event of blood exposure, but this has not been empirically determined (21).

The rates of HIV prevalence and incidence vary greatly among IDUs throughout the world (22). There are many populations of IDUs where HIV has not yet been introduced (23). In other regions, HIV in IDUs has stabilized at a relatively low prevalence (less than 5%) (24–28); incidence is also typically low in these settings, with rates of 1/100 person-years at risk or less (29, 30). There are also examples of IDU populations (e.g., Bangkok and Amsterdam) where seroprevalence appears to have stabilized at high levels, from 20–50% (31–33); under these conditions, HIV incidence is generally in the range of 4–8 per 100 person-years at risk (34, 35). Finally, there are some populations (China, Myanmar, and northeast India) in which HIV has infected a majority of IDUs (80% or more) (36, 37), and incidence rates may be 10/100 person-years at risk or higher (38, 39). Rapid dissemination of HIV appears to be most common in populations in which there is little or no awareness of the threat or consequences of HIV. Documented historical examples of the rapid spread of HIV include New York City and Edinburgh; in each case, a shift from very low or no HIV infection in IDUs to moderate (20–40%) prevalence occurred over a period of six months to two years (40, 41). These early experiences, together with more recent examples, suggest that low HIV-seroprevalence patterns can change abruptly.

Variability in HIV incidence and prevalence rates among different populations of IDUs appears to be due to multiple factors, including: how long HIV has been present in the local population; the underlying frequency of risk behaviors; existing "mixing patterns" among local IDUs; and the extent to which public health and community leaders have implemented effective HIV-prevention programs. Understanding this variability and implementing suitable HIV-prevention programs are the two current, pressing challenges in controlling the transmission of HIV among IDUs.

Natural History and Epidemiology of HCV among IDUs

Hepatitis C virus infection becomes persistent in 70–80% of cases, as determined by persistently abnormal serum enzymes and/or viremia (HCV-RNA) (42). In a study of 43 IDUs in whom recent infection was observed, viral persistence was noted in 86%, after an average follow-up of six years (43). Persistent infection is believed to occur as a result of rapid genetic mutation of HCV and immune escape (44). Reinfection with the same or a different strain of HCV has been demonstrated experimentally in chimpanzees and observed to occur in humans with repeated exposure to HCV (45, 46). Thus, in the majority of cases, the immune response to HCV confers no protection against the development of chronic infection (47).

Following infection, 25–50% of IDUs develop acute hepatitis, with only one-half of symptomatic patients manifesting jaundice. More than 60% of persistent infections result in chronic liver disease; cirrhosis or chronic active hepatitis occurs within several years after infection in most (40–70%) of these cases (48). Persistent HCV infection is also associated with hepatocellular carcinoma (HCC) (49, 50). Few natural history studies have been carried out to determine whether ongoing drug use influences the course of persistent HCV infection (51). However, alcohol use is consistently associated with more rapid progression and greater severity of liver disease in patients with HCV infection (52). HCV-genotype may also affect the course of the disease (53).

At present, alpha-interferon alone or in combination with Ribavirin is the only drug licensed for treatment of HCV infection (54). Early trials indicated that alpha-interferon treatment resulted in a sustained virological response (viral clearance six months post-treatment) in only 20% of cases (54); the combination of Ribavirin with interferon treatment raised the response level to approximately 40% (55). Protease inhibitors are also being evaluated as a treatment for HCV infection (56).

Studies of the prevalence of HCV infection carried, out in IDU populations where drug injection has become endemic, support the hypothesis of rapid penetration. Compared to the epidemiology of HIV, there is relatively little heterogeneity in anti-HCV seroprevalence. Seroprevalence has been reported in a fairly narrow range, of 50–95% (57). The incidence of HCV infection in IDUs previously seronegative for HCV-antibody (anti-HCV) is generally 10–100 times higher than HIV incidence in the same group, in the range of 10–30% per year (57). These studies include 9% per year in Rome (58), 12% in Geneva (59), 17% in Seattle (60), and 38% in Australia (61).

There are many factors suggesting that, in a population of IDUs, a pattern of endemic HCV infection tends to develop over a relatively short period of time. Indeed, host, viral and environmental factors that determine transmission patterns of infectious diseases all seem to favor rapid spread of HCV among IDUs (62). Viral factors that facilitate HCV dissemination include the relatively high efficiency of HCV transmission via blood exposure; studies of needlestick exposures to contaminated syringes in health-care settings show that HCV transmission occurs in 3% of such exposures vs. 0.3% for HIV (63). As a result of the high levels of persistent infection in HCV-exposed individuals, there are large reservoirs of HCV-infectious IDUs in many regions of the world (57). The size of the reservoir of HCV infection may be a significant environmental factor affecting transmission dynamics, since it is related to the probability of contact with an infected individual. Host factors include behaviors that expose individuals to HCV, such as the shared use of drug preparation and injection equipment. Declines in these risk practices have been observed in the era of HIV/AIDS, and associated with reductions in HIV incidence (64). However, injection risk behavior has not been eliminated (65–67), and sharing of drug preparation equipment such as drug cookers and filtration cotton, seems to persist in IDU populations because it is believed to be low risk in terms of HIV transmission (68). Thus, persistent risk behavior in IDUs, in combination with HCV viral and environmental factors that promote transmission, appears to be sufficient to facilitate the spread of HCV. One can imagine HCV spreading nearly unimpeded in a population of IDUs; such a scenario would also be possible for HIV, with some important differences. The lower transmission efficiency for HIV may impede its spread. Moreover, as a consequence of the lower HIV transmission efficiency, any reduction in syringe-sharing would be reflected in fewer HIV transmissions.

A vaccine against HCV infection might interrupt the chain of its transmission and reduce the number of new infections. However, some of the same problems exist as with HIV vaccine development. These include the existence of multiple strains and the high mutation rate of the HCV genome (69). While there is some current research to develop an HCV vaccine, the prospect of having such a vaccine in the immediate future is unlikely.

Comparison of HIV and HCV Prevention among IDUs

There have been more than fifteen years of efforts to prevent HIV infection among injecting drug users. To date, all efforts to prevent transmission of HIV and other blood-borne viruses among IDUs have led to risk reduction without total risk elimination. The extent of risk reduction appears to have been sufficient to significantly decrease HIV transmission among IDUs in many different areas (25, 70). And in some cities, low HIV prevalence has been maintained for more than five years. There is also new evidence that risk reduction programs may be able to "reverse" high seroprevalence HIV epidemics, such as the HIV epidemic among IDUs in New York City (64).

In contrast, awareness of the problem of HCV infection in IDUs arose only recently (71). At present, there is only one published study showing that a risk reduction program (needle exchange) was associated with reduced HCV infection in IDUs (72). Other studies have reported that neither drug treatment (73) nor needle exchange (58) had any effect on HCV incidence. Moreover, there is no evidence on a community level that risk reduction programs can control HCV within a population of IDUs. Indeed, there are no known populations where HCV prevalence has remained at less than 5% for any considerable period of time. The reasons for this are not fully understood, and direct comparisons of HIV and HCV incidence in IDU samples has not provided an explanation (29, 32, 59–61). Thus, HCV control may be far more difficult to achieve than HIV control in a community of IDUs, and HCV prevention may be viewed as a relatively high standard against which public health prevention programs may measure themselves.

Summary

Throughout the fifteen years of HIV prevention efforts, there have been notable successes in terms of individual IDUs who did not become infected, in terms of prevention programs that were effective with large numbers of IDUs, and in terms of populations of IDUs in which both prevalence and incidence rates have remained very low. There are also many areas of the world where HIV is spreading very rapidly among drug injectors. The greatest problem in those areas may be the failure of public officials to implement prevention programs of known effectiveness.

In contrast, programs that explicitly attempt to reduce HCV transmission among IDUs have only existed a few years. To date, there have been few documented successes in reducing HCV transmission. Programs that can effectively control HIV transmission appear to be less effective against HCV, and a new generation of prevention efforts may be needed to control HCV transmission. This may be a formidable challenge, requiring greater resources in terms of outreach education, and distribution or exchange of sterile syringes and other drug injection equipment among IDUs. However, it is quite likely that HCV prevention efforts will benefit considerably from previous successes in developing and implementing programs to control HIV transmission among IDUs. Finally, HIV and HCV are but two blood-borne pathogens for which injecting drug users are at high risk. The lessons learned in HIV prevention and to be learned in HCV prevention must be kept in mind for future, as yet unrecognized, blood-borne infectious diseases.

Acknowledgments

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Interactions between Methadone and Medications Used to Treat HIV Infection:

A Review

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Abstract

Background: It is critical for providers caring for HIV-positive methadone recipients to have accurate information on pharmacologic interactions between methadone and antiretroviral therapy. If providers do not have these data, symptoms of narcotic withdrawal or excess due to medication interactions may be mismanaged, and antiretroviral regimens may be suboptimal in efficacy or associated with increased side effects and toxicities. This review was undertaken to clarify what is known about interactions between pharmacotherapies of opiate dependence and HIV-related medications, to suggest clinically useful approaches to these issues, and to outline areas which need further study.

Methods: A search for relevant published papers and abstracts presented at scientific meetings was conducted using electronic databases. These documents were obtained and reviewed, and additional publications referenced in them were also reviewed.

Results: Pharmacokinetic interactions between methadone and zidovudine, didanosine, stavudine, abacavir, nevirapine, efavirenz and nelfinavir have been documented. The mechanisms, clinical implications and management of these interactions are reviewed.

Conclusions: Interactions between methadone and some HIV-related medications are known to occur, yet their characteristics cannot reliably be predicted based on current understanding of metabolic enzyme induction and inhibition, or through *in vitro* studies. Only carefully designed and conducted pharmacologic studies involving human subjects can help us define the nature of the interactions between methadone (and other pharmacotherapies for opiate dependence) and specific HIV-related medications. Clinicians must be aware of known interactions and be alert to the possibility that interactions which are still undocumented may be present among their patients.

Key Words: Methadone, antiretroviral therapy, interactions, HIV, medications, pharmacotherapies, pharmacodynamics.

Introduction

IN THE UNITED STATES, injection drug use is the second most common risk behavior which results in acquired immunodeficiency syndrome (AIDS), and it remains a driving force in the epidemic. Treatment for substance abuse, particularly opiate abuse, is often a critical component of AIDS prevention and treatment. Methadone, an orally administered, long-acting opiate, is an effective and widely accepted pharmacotherapy used in the treatment of heroin dependence (1). According to a survey in 1998 by the American Methadone Treatment Association, of the 179,000 people receiving methadone therapy in the United States, approximately 25–30% are infected with HIV. Most of the latter group are eligible for treatment with antiretroviral agents and other HIV therapies.

Injection drug users, who have been underrepresented in clinical trials of HIV therapies (2), may be at greater risk for toxicity from antiretroviral medications because of the high prevalence in this population of hepatic, renal, neurologic, pancreatic, and hematologic disease (3). Drug users' care is further complicated by the fact that so little is known about potentially important interactions between HIV therapies and illicit substances. It is becoming apparent, however, that significant interactions exist between certain HIV therapies and pharmacotherapies used to treat substance abuse. Only recently has attention been directed to the study of potential interactions between HIV-related medications and substances of abuse and their treatments, which can influence the success of either or both treatment.

It is critical for providers caring for HIV-positive methadone recipients to have accurate information on the interactions between methadone and antiretroviral therapy. There are now fourteen antiretroviral medications approved for treat-

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ing HIV infection, and others are expected soon. Knowledge of the interactions between these medications and the pharmacotherapies for opiate dependence taken by patients may influence doctors' initial and subsequent choice of antiretroviral regimens. In addition, the interpretation of patients' signs and symptoms, particularly those of narcotic withdrawal ("that HIV pill is eating my meth") or excess ("my meth is feeling too strong on these HIV pills") may be influenced by knowledge of such interactions. Without thoughtful responses by clinicians to such symptoms, patients may implement their own potentially harmful interventions, such as using additional heroin, or avoiding or discontinuing the medication(s) believed to be at fault — thereby risking ineffective treatment and development of antiretroviral resistance (4).

The purpose of this review, therefore, is to examine and discuss what is known about the interactions between methadone and the many medications used to treat HIV infection. Earlier reviews did not provide information on the different classes of antiretroviral medications (5), or were published before the results of several important recent studies had been completed (6). Although this discussion will focus on interactions between methadone and antiretroviral medications, consideration will also be given to interactions with other HIV-related medicines.

Methods

A search for relevant published papers and abstracts presented at scientific meetings was conducted using the National Library of Medicine's Medline and AIDSLine databases; these documents were obtained and reviewed. Additional references listed in the literature obtained were also reviewed. In addition, responses from the manufacturers of antiretroviral medications to requests for data on the interactions of their products with methadone were received and incorporated into this review.

Overview of Hepatic Metabolism

Metabolism of drugs by the liver may be viewed as occurring in two phases. In Phase I, compounds are chemically altered (e.g., oxidized, reduced, hydrolyzed) by one of the cytochrome P450 enzymes. Fourteen distinct families of cytochrome P450 enzymes have been identified (CYP 1, CYP 2, CYP 3, etc.), each with subfamilies (CYP 3A, CYP 3B, etc.) and specific gene products within subfamilies (CYP 3A3, CYP 3A4, etc.). A medication may affect the Phase I metabolism of another medication in several ways. The first drug may diminish the Phase I metabolism of the second drug by competitively inhibiting the CYP 450 enzyme(s) responsible for the second drug's metabolism. Alternatively, the first drug might accelerate Phase I metabolism of the second drug by inducing additional synthesis of the CYP 450 isoform(s) involved in the second drug's metabolism. In Phase II of hepatic metabolism, a compound is altered by being coupled (e.g., conjugated) with another moiety to yield an inactive metabolite.

Methadone Metabolism

Methadone is dosed orally, once daily. With a half-life of 24–36 hours, it takes approximately 3 days at the same dose to achieve steady state levels. Methadone undergoes hepatic biotransformation by the cytochrome P450 system. Two cytochrome P450 isoenzymes, CYP 3A4 and CYP 2D6, appear to be primarily involved in this process, with CYP 2C possibly playing a minor role as well (7, 8). *N*-demethylation of methadone results in the formation of metabolites, which are excreted in the urine and bile (9). Some unmetabolized methadone is also excreted in the urine, with a ratio of excreted metabolites to excreted unmetabolized methadone of between 5:1 and 1:1 (9). It is likely that substantial interindividual variation (up to 20-fold) in the amount of CYP 3A4 expressed in the liver accounts, at least in part, for uneven correlations between methadone dose and methadone plasma concentration in different persons. Interactions between methadone and inducers of CYP 3A4 such as rifampin (10) result in more rapid metabolism of methadone (11), whereas CYP 3A4 competitive inhibitors like diazepam (12) or fluvoxamine (13) may potentiate methadone's effect. In addition to being a substrate of the cytochrome P450 system, methadone may also act as a partial inhibitor of the CYP 3A4 and CYP 2D6 isoenzymes (13).

Metabolism of Antiretroviral Medications

Nucleoside reverse transcriptase inhibitors (NRTIs) do not appear to be inducers or inhibitors of the cytochrome P450 system (14). Zidovudine (AZT) is glucuronidated, and didanosine (ddI), zalcitabine (ddC), lamivudine (3TC), and abacavir (ABC) primarily undergo renal excretion. Animal studies suggest that renal excretion and cleavage to thymidine are principal routes by which stavudine (d4T) is cleared.

By way of contrast, the non-nucleoside reverse transcriptase inhibitors (NNRTIs) and protease inhibitors (PIs) share metabolic pathways with methadone, leading to the possibility that important interactions might occur between methadone and these medications. NNRTIs have complex interactions with the cytochrome P450 system. Nevirapine is an inducer of CYP 3A which then causes diminished levels of medications metabolized by this cytochrome P450 subfamily (15). Nevirapine is also metabolized by CYP 3A4 and CYP 2B6 and, to a far lesser degree, by CYP 2D6. Delavirdine is a moderately potent CYP 3A inhibitor and may therefore raise concentrations of other medications metabolized by this isoform. It is metabolized by CYP 3A4 and CYP 2D6 (14). Efavirenz both induces and inhibits CYP 3A4, and is metabolized *in vitro* by CYP 3A4 and CYP 2B6 (16).

Protease inhibitors (PIs) are metabolized primarily by the 3A4 isoform of the cytochrome P450 system (17). In addition, the PIs inhibit CYP 3A4: ritonavir most potently; indinavir, nelfinavir and amprenavir all somewhat less intensely; and saquinavir the least of all (17, 18). Each PI has a unique profile of induction and inhibition of, and metabolism by, specific cytochrome P450 isoforms.

Interactions between Methadone and Antiretroviral Medications

1. NRTIs

Researchers have performed detailed pharmacokinetic studies of the interaction between AZT and methadone in human subjects (19, 20). Methadone administration increased the area under the AZT concentration-time curve (AUC) by approximately 40%. Methadone appeared to exert this effect by means of inhibition of AZT glucuronidation and, to a lesser extent, by decreasing renal clearance of AZT. Although AZT side effects are dose related, the clinical significance of the increase in AZT AUC in patients receiving methadone is unclear. Formal study of AZT-related toxicities in this population has not been performed and would be difficult. Persons receiving both methadone and AZT may experience symptoms that are characteristic of opiate withdrawal, such as headache, muscle aches, fatigue, and irritability, and may attribute these symptoms to reduced methadone levels ("this AZT is eating my meth"). It is noteworthy, however, that the AZT and methadone pharmacokinetic interaction studies determined that AZT has no effect on plasma methadone levels. It is, therefore, more likely that such symptoms are side effects of AZT — perhaps occurring more frequently and with greater severity as a result of the patient's increased AZT exposure — rather than indications of AZT-induced methadone withdrawal.

Results from studies with d4T and ddI were reported at the Sixth Conference on Retroviruses and Opportunistic Infections in 1999 (21). Fifteen patients receiving long-term methadone treatment alternatively received ddI (200-mg tablet BID), and d4T (40 mg BID). Pharmacokinetic parameters were compared with a matched control group of 10 patients who were not on methadone but who received the same NRTIs. Neither ddI nor d4T affected methadone levels. However, methadone appeared to alter the disposition of both NRTIs. Methadone decreased the AUC for d4T by 18% and the maximum concentration (Cmax) by 39%. These values are unlikely to be of clinical significance. However, methadone decreased the AUC for ddI by 60% and the Cmax by 64%. These results suggest that an increase in ddI dosage may be indicated in patients who are also treated with methadone. The likely mechanism is decreased absorption of the tablet formulation resulting from methadone-induced delay in gastric motility. Further study is needed to determine if this effect is confined to the tablet formulation or if similar effects will be seen with other ddI preparations. This issue is particularly important because of evidence that ddI can be dosed once daily, making it an excellent candidate for inclusion in a regimen of directly observed antiretroviral therapy in methadone programs (22).

Pharmacokinetic data regarding the interaction between methadone and abacavir, which like zidovudine is metabolized by glucuronidation, were presented recently by Sellers and colleagues (23). Nineteen patients entering methadone treatment were given a single dose of abacavir (600 mg) on day 1, begun on methadone and brought to a "steady state" dose on days 2 – 14, and then co-administered abacavir and methadone on days 15 – 28. Pharmacokinetic sampling was performed on days 1 and 15 (for abacavir) and on days 14 and 28 (for methadone). Seven patients did not complete the study. The authors report a statistically significant increase (23%) in the rate of clearance of methadone from day 14 to day 28, but no changes in the time to peak concentration, half-life ($t_{1/2}$) or renal clearance of methadone. In addition, they observed a significant decrease (34%) in the peak concentration and increase (67%) in the time to peak concentration of abacavir from day 1 to 15, but no changes in the overall clearance, renal clearance, or $t_{1/2}$ of abacavir. The clinical relevance of these findings is unclear. While the delay in time to peak concentration of abacavir could plausibly be due to the inhibiting effect of methadone on gastric motility, it is not clear whether the changes observed were in fact due to methadone-abacavir interactions or to other factors, such as other medications participants may have been taking. Confirmation of these findings with data regarding patient symptomatology is needed before clinically grounded conclusions can be drawn from these data.

A formal study of a single dose of lamivudine (150 mg) combined with zidovudine (300 mg) demonstrated no effect on methadone levels (24).

2. NNRTIs

A recent case series (25) lends further support to substantial anecdotal evidence that nevirapine appears to precipitate symptoms of narcotic withdrawal in methadone-maintained patients. Seven patients receiving nevirapine experienced methadone withdrawal, which was corrected by either discontinuing nevirapine or increasing the methadone dose. Three of these episodes were documented by low trough methadone levels. A methadone-nevirapine interaction was also suggested by data presented by Staszewski et al. (22) from a study of once-daily antiretroviral therapy among drug users in Germany. Among patients maintained on methadone who started nevirapine, an average 45% increase in methadone dose was required to counter the associated withdrawal symptoms.

The results of investigations presented recently by Clarke and colleagues (26) provide pharmacokinetic data to support the clinical observations detailed above. Ten dose-stabilized methadone maintenance patients were started on antiretroviral therapy with nevirapine and two nucleosides. From baseline to approximately three weeks following nevirapine initiation, the mean methadone AUC decreased by 46%.

A recently presented and similarly retrospective case series offers evidence suggesting that, as with nevirapine, initiation of an efavirenz-containing antiretroviral regimen also necessitated increased methadone doses in most patients (27). In this study, nine methadone-maintained patients were followed after initiation of antiretroviral therapy. Seven of the nine patients were taking efavirenz-containing regimens, and six of these (87%) had a resumption of heroin use that resulted in a methadone dose increase, presumably in response to efavirenz-induced withdrawal symptoms. Such findings underscore the clinical urgency of recognizing interactions of this and other medications with methadone.

Further evidence of an efavirenz-methadone interaction derives from the pharmacokinetic data presented by Clarke and colleagues (26). Fifteen dose-stabilized methadone maintenance patients were started on antiretroviral therapy with efavirenz and two nucleosides. From baseline to three weeks following efavirenz initiation, mean methadone peak plasma concentration and AUC decreased by 48% and 57%, respectively. Of the 25 patients begun on nevirapine or efavirenz-containing regimens presented by Clarke et al., 17 (68%) complained of narcotic withdrawal symptoms, necessitating a mean increase in methadone dose of 21%.

To date, no data have been reported regarding interactions between methadone and delavirdine. One might predict, based on delavirdine's inhibition of CYP 3A4, that if delavirdine were to affect methadone it might potentiate, rather than attenuate, its effectiveness.

Methadone and Protease Inhibitors

In vitro data support the possibility that PIs might influence methadone metabolism. Using a hepatic microsomal preparation derived from healthy human volunteers, researchers demonstrated that methadone N-demethylation was inhibited by ritonavir, indinavir, and saquinavir. Ritonavir had the greatest effect, followed by indinavir and then saquinavir. These *in vitro* findings suggest that PIs might retard methadone metabolism, and thus increase methadone levels, in persons taking these medications together (28).

Ritonavir was the first PI investigated and reported in human interaction studies with methadone. In a manufacturer-sponsored study using volunteers who were not addicted to opiates, a dose of 20 mg of methadone was administered on day one (29). After a 14-day "methadone washout" period, ritonavir was administered twice daily on days 15 to 28. On day 25, a single dose of only 5 mg of methadone was administered. The extremely low second dose of methadone was chosen because the non-addicted volunteers had difficulty tolerating the initial 20 mg dose. Researchers studied the effect of ritonavir on methadone levels by comparing "dose-adjusted" methadone levels after the first (20 mg) and second (5 mg) methadone doses. The authors calculated a 36% decrease in the methadone AUC and a 38% decrease in peak methadone concentration in volunteers on ritonavir, an unexpected result, and given the flaws of the study design, one which is uninterpretable and not possible to relate to clinical practice. The effect of methadone on ritonavir levels was assessed by comparing ritonavir levels in the absence of methadone with those following the 5-mg methadone dose on day 25. No effect on ritonavir concentrations was observed. Further study with long-term methadone patients receiving therapeutic doses of methadone is essential before any firm conclusions can be drawn about interactions between ritonavir and methadone.

Recent pharmacokinetic data shed light on the interaction between nelfinavir and methadone (30). Fourteen patients on stable methadone doses were monitored before, during and after an 8-day course of nelfinavir (1250 mg twice daily). From baseline (immediately prior to nelfinavir initiation) to day eight of nelfinavir, mean methadone peak plasma concentration and AUC decreased by 43% and 40%, respectively. Yet not one of the patients reported withdrawal symptoms or needed methadone dose adjustment during or after the study. In addition, a retrospective chart review of 36 patients on stable methadone doses prior to initiation of nelfinavir-containing antiretroviral therapy found no evidence of withdrawal symptoms or methadone dose adjustments in 34 patients (one patient required an increase and another a decrease). The seeming discrepancy between reduced methadone levels and absence of withdrawal symptoms and signs requires confirmation. Nelfinavir levels in patients receiving methadone did not differ significantly from historical levels in patients not taking other medications.

Study of the interaction between methadone and saquinavir is planned. AIDS Clinical Trials Group (ACTG) protocol 401 has been designed to investigate the effect of the combination of ritonavir and saquinavir on methadone levels.

Interactions between Methadone and Other HIV-Related Medications

It is well known that rifampin, a potent inducer of CYP 3A4, increases the metabolism of methadone (11). Co-administration is associated with a 33–68% decrease in plasma methadone levels. When effective clinical alternatives exist, rifampin should not be administered to patients receiving methadone. However, if it is necessary to treat a methadone-maintained patient with rifampin, as it may be for some cases of active tuberculosis, it is essential that the patient's methadone dose be raised as needed, to maintain adequate suppression of narcotic withdrawal symptoms. Rifabutin induces CYP 3A4, but far less potently than does rifampin. As a result, rifabutin has been suggested as an alternative tuberculosis treatment medication when interaction between rifampin and methadone or a PI is expected or observed (31). A study of the effect of rifabutin in methadone-maintained persons found no change in methadone levels or pharmacokinetics during rifabutin administration (32). Although some symptoms of narcotic withdrawal were reported by the majority of participants during rifabutin co-administration, these symptoms were not associated with any effect of rifabutin on methadone levels.

Azoles may inhibit CYP 3A4. Researchers have investigated the interaction between fluconazole and methadone. Twenty-five patients receiving methadone maintenance were randomly assigned to receive oral fluconazole or placebo for 14 days. A 30% increase in the methadone AUC was observed among participants receiving fluconazole (33). However, no signs or symptoms attributable to narcotic overdose were observed among this group, and the clinical significance of this interaction remains unclear.

Seizure disorders are common among opiate-dependent persons, and the interactions between anti-epileptic medications and methadone have been investigated. Phenytoin (34), phenobarbital (35), and possibly carbamazepine (36) induce varying degrees of opiate-withdrawal symptoms among methadone-maintained patients. Of the medications studied, only valproic acid has not been demonstrated to influence patients' methadone dose needs (36).

Several other therapies for opiate abuse are currently available and may be used increasingly in the future. These include LAAM (levo-alpha-acetylmethadol) and buprenorphine. LAAM is metabolized in a manner similar to that of methadone, and buprenorphine is excreted unchanged in the urine. One can thus speculate that interactions demonstrated with methadone are likely with LAAM, and may not occur with buprenorphine. However, preliminary data suggest that, unlike methadone, LAAM may not potentiate zidovudine levels, and that contrary to expectation, buprenorphine might actually reduce zidovudine exposure (37). Because such interactions could influence the opiate-abuse treatment selected for patients on antiretroviral therapies, and because these between-medication interactions do not always occur as predicted, careful study of medication interactions involving these newer agents is essential.

Data regarding the interaction between ritonavir and the narcotic analgesic meperidine were presented at the Sixth Conference on Retroviruses and Opportunistic Infections (38). Meperidine pharmacokinetics were assessed after a single 50-mg oral dose in eight HIV-negative subjects. Twice daily administration of ritonavir was then initiated and continued for 10 days, at which time a 50-mg dose of meperidine was again administered, and meperidine and ritonavir pharmacokinetics reassessed. Ritonavir administration was associated with a 67% decrease in the meperidine AUC, apparently caused by ritonavir-induced increases in meperidine metabolism. Ritonavir levels were not affected by meperidine administration. These data contrast with the warning in the ritonavir package insert that, because of its CYP 3A4 inhibition, ritonavir might boost meperidine levels and that the two drugs should therefore not be co-administered. Such data further emphasize the need for specifically designed studies to investigate the potential interactions between opiates and HIV-related medications. In this instance, increases in opiates used for pain medication are likely to be required for patients receiving ritonavir.

The interactions between methadone and the medications discussed in the preceding sections are summarized in the Table.

Clinical Comments

Several points deserve emphasis. It is now known that interactions occur between methadone and some HIV-related medications, yet their characteristics cannot reliably be predicted based on current understanding of enzyme induction and/or inhibition, or through *in vitro* studies. Carefully designed studies using human subjects are urgently needed. Until more data are available, clinicians are left to rely on their best judgment when selecting regimens and when clinical evidence of possible interactions arises in the course of patient care. As always, much is gained from listening to the patient. If a methadone-maintained patient recently started on HIV-related medication, particularly an NNRTI, describes withdrawal symptoms, and no other reason for such symptoms is evident, an empiric trial of raising the methadone dose may be an appropriate response. Methadone dose increases should be in 10-mg increments. If marked withdrawal is present and attributable to a medication interaction in a previously stable methadone-maintained patient, an incremental increase of 20 mg may be considered. To avoid overdosing, however, methadone should not be increased more frequently than every two to three days. Alternatively, use of a different antiretroviral agent might be warranted. Obtaining a trough methadone level to establish whether withdrawal symptoms are indeed due to increased methadone metabolism may be useful in selected cases, particularly if continuation of an HIV therapeutic regimen is deemed necessary. If a patient on AZT and methadone is experiencing side effects and possible withdrawal symptoms, reduction in AZT dose may be appropriate before the methadone dose is altered. If drowsiness or other symptoms of methadone excess are reported, reduction in methadone dose might be considered, following documentation with a trough methadone level.

Further research is needed to elucidate the clinical significance of the changes in methadone levels observed in the types of pharmacokinetic studies described above. For example, narcotic withdrawal symptoms did not accompany the 40% reduction in methadone level among patients receiving nelfinavir; yet frequent symptoms were reported by patients with decreases of similar magnitude in plasma methadone levels caused by efavirenz. This difference in findings might be explained if these medications had differential influences on the percent of methadone that is protein bound (30). Thus, it is possible that one might have to measure free methadone levels, not the combined free and protein-bound levels measured in most assays, to understand such differences. However, this has not yet been studied. For now, investigators of interactions between opioid pharmacotherapies and antiretroviral medications must perform standardized assessments of narcotic withdrawal symptoms in their subjects to define the clinical significance of the changes in blood levels they report.

The delay in the appearance of symptoms due to medication interactions can be highly variable. Inhibition of cytochrome P450 enzymes can occur as soon as an inhibiting medication is started, with associated symptoms appearing shortly thereafter. Induction and increased production of P450 isozymes follows a more prolonged period, typically ranging from 10 to 21 days. Such dynamics notwithstanding, it is not uncommon for a patient who has been on methadone and a stable antiretroviral regimen for a month or longer to report symptoms of methadone lack or excess. When other reasons for such symptoms cannot be discerned (e.g., thyroid dysfunction, new onset of cocaine use, etc.), an empiric change in the methadone dose may be indicated, with careful follow-up to see if this helps. Clinicians must not be reluctant to attempt such interventions in the absence of definitive data regarding the interactions between the medication in question and methadone. In addition to the direct therapeutic value of such interventions, evidence that the provider takes the patient's complaint seriously often builds valuable trust in the doctor-patient relationship.

TABLE

Interactions between HIV-Related Medications and Methadone — An Overview

Medication	Formally Studied?*	Effect on Methadone	Effect on HIV-Related Medication
NRTI			
Zidovudine (AZT)	Yes	None	↑ AZT AUC by 40%
Didanosine (ddI)	Yes	None	↓ ddI AUC by 60%
Zalcitabine (ddC)	No	Not studied or reported	Not studied or reported
Stavudine (d4T)	Yes	None	↓ d4T AUC by 18%
Lamivudine (3TC)	Yes	None	Not studied
Abacavir (ABC)	Yes	↑ Methadone clearance	↑ Time to peak concentration ↓ Peak concentration.
NNRTI			
Nevirapine	Yes	Withdrawal symptoms ↓ Methadone levels by 46% Need for ↑ methadone dose observed	Not studied or reported
Delavirdine	No	↑ Methadone levels predicted	Not studied or reported
Efavirenz	Yes	↓ Methadone levels by 48% Heroin use relapse Need for ↑ methadone dose observed	Not studied or reported
PI			
Indinavir	No	Not reported	Not studied or reported
Ritonavir	Yes	↓ Methadone levels reported † ↓ Meperidine levels	No effect reported †
Nelfinavir	Yes	↓ Methadone levels, but no withdrawal symptoms observed	No
Saquinavir	Planned	Not studied or reported	Not studied or reported
Amprenavir	In progress	Not yet available	Not yet available
Other medications used in the treatment of HIV-infected persons			
Rifampin	Yes	↓ Methadone levels, often sharply	None reported
Rifabutin	Yes	No change in methadone levels Mild narcotic withdrawal symptoms	None reported
Fluconazole	Yes	↑ Methadone levels by approximately 30%, clinical significance unknown	None reported
Phenytoin	Yes	↓ Methadone levels, often sharply	None reported
Phenobarbital	Yes	↓ Methadone levels, often sharply	None reported
Carbamazepine	Yes	↓ Methadone levels	None reported

NRTI = nucleoside reverse transcriptase inhibitors
NNRTI = non-nucleoside reverse transcriptase inhibitors
PI = protease inhibitor
AUC = area under curve
* See text for references.
† Study design limits clinical utility of results.

Conclusions

Only carefully designed and conducted pharmacologic studies of human subjects can help define the nature of the interactions between methadone (and other pharmacotherapies for opiate dependence) and specific HIV-related medications. Clinicians must be informed of those interactions documented thus far, and remain alert to the possibility that other interactions, which are still undocumented, may be present among their patients. Where not already initiated, studies must be promptly undertaken to generate clinically useful data to help clinicians provide optimal care to HIV-infected persons receiving pharmacotherapies for opiate dependence.

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The Impact of Hepatitis C Virus Infection on Methadone Maintenance Treatment

David M. Novick, M.D.

Abstract

Hepatitis C virus infection is now recognized as a common and serious complication of injection drug use and will be encountered frequently in methadone maintenance patients. Approximately 1.8% of the United States population, or 3.9 million persons, are infected with hepatitis C virus. A majority of acute hepatitis C virus infections are associated with injection drug use, and 64–88% of injection drug users in seroprevalence studies have antibodies to hepatitis C. Hepatitis C virus infection is almost always chronic, and alcohol use increases the clinical severity. Therapy with interferon and ribavirin will induce long-term remission in up to 43% of patients with hepatitis C virus infection. Proper diagnosis and treatment of hepatitis C virus infection will be indicated for many patients in methadone programs and will require considerable resources.

Key Words: Hepatitis C, methadone; heroin, injection drug use, alcoholism, epidemiology.

METHADONE MAINTENANCE is the most effective method for achieving sustained remission of chronic opiate use (1). Almost all patients in methadone programs have been injection drug users, and as such have been at risk for numerous medical complications (2). In the 1990s, chronic hepatitis C virus (HCV) infection became increasingly recognized as a widely prevalent and potentially serious disease in injection drug users and methadone maintenance patients. This article reviews the features of HCV infection of greatest relevance to methadone maintenance patients and discusses the impact of increasing numbers of HCV-infected patients in methadone programs.

Virology

Although the existence of HCV was well established in the 1970s, its identification in the late 1980s was possible only after newer techniques of molecular biology became available (3, 4). Our knowledge of the molecular structure and features of HCV has expanded rapidly(4, 5). One important feature of HCV is sequence heterogeneity, which is more prominent in certain regions of the genome, such as areas encoding the envelope proteins (5). Genetic variability in this RNA virus has been manifest as genotypes and quasispecies. Genotypes are major groups of HCV strains, of which six major types and more than 50 subtypes have been described (5, 6); these differ in prevalence in different geographic locations and may influence clinical manifestations and response to therapy. Quasispecies are a heterogeneous but closely related group of viral sequences. They may be extremely complex, with 19 unique sequences having been isolated from one single patient (7). Viruses such as HCV, which form quasispecies, can develop mutations within an infected individual which escape the host's immune response of neutralizing antibodies

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and cytotoxic T cells (4, 5). Quasispecies thus contribute to the very high frequency of chronic infection in HCV and render many potential vaccines ineffective.

Epidemiology

HCV has now been recognized as a major public health problem in the United States and elsewhere (8, 9). It is estimated that 1.8% of the U.S. population, or 3.9 million persons, are infected with HCV (8). The number of newly acquired cases of HCV was stable during the 1980s, but declined by more than 80% in the first half of the 1990s. This decline has been associated with a marked decrease in new infections in injection drug users (8). Nevertheless, injection drug users still comprise the single largest risk group for HCV. In data from the period 1991 – 1995 (8), 43% of cases of acute HCV were injection drug users; another 16% had past injection drug use; and 5% snorted cocaine. Others had a low socio-economic status; only 1% had no identifiable risk factor. With approximately 8,000 – 10,000 deaths occurring each year from HCV-associated chronic liver disease, HCV is now the most common indication for liver transplantation (10). The death rate from HCV is expected to increase markedly over the next decade as the population of infected persons ages.

Most injection drug users will become infected with HCV (2). In recent seroprevalence studies (11, 12), 64 – 88% of such persons had antibody to HCV (anti-HCV). In one study, 73% of injection drug users and 4% of oral drug users were HCV seropositive (13). HCV infection is usually acquired early in the patients' drug injecting careers (14, 15). Among persons injecting for one year or less, 77% had anti-HCV (15). HCV may be acquired after only a few injections, as in the weekend "recreational" user. Anti-HCV was found in 94% of persons who had injected drugs for 10 years or longer (14) and in 98% of injection drug users with chronic liver disease (16). By the 1970s, HCV had become well established in populations of injection drug users in New York City (16) and Victoria, Australia (17). A variety of HCV genotypes have been described in injection drug users (2), with type 1 the most common in the United States (18).

Sexual transmission of HCV occurs infrequently (19), and sexual practices have not correlated significantly with HCV seroprevalence in injection drug users (14). However, HCV-positive persons infected with human immunodeficiency virus (HIV) are much more likely to transmit HCV to a sexual partner (20, 21).

Several studies have addressed the incidence of HCV in injection drug users. Among 142 such persons in Baltimore who were susceptible to HCV, 43 (30%) became HCV-positive during a 6.5-year follow-up (22). Over the 8-year study period (1988 – 1996), the overall incidence of HCV infection was 6.4 cases per 100 person-years. The HCV incidence rate declined significantly during the study, however, with a rate of 13.4 cases per 100 person-years in 1988 – 1990 but only 2.3 in 1991 – 1996. The authors suggest that this marked decline is due to a saturation of the at-risk population rather than a reduction in high-risk behavior (22). In their study, frequent drug use and needle sharing were associated with seroconversion to HCV. In an Australian study, the overall incidence of anti-HCV seroconversion among injection drug users was 10.7 cases per 100 person-years (23). A decline in incidence was also seen but was not significant. Some subpopulations of injection drug users in Australia, e.g., young male prison entrants, have had HCV incidence rates as high as 41 cases per 100 person-years, albeit this was only in a small sample (24).

Studies conducted in methadone maintenance programs have yielded results similar to those in the studies of injection drug users cited above. The seroprevalence of HCV in methadone patients ranges from 67 – 84% (25 – 28). HCV incidence rates in three studies of methadone programs were 11, 12, and 22 cases per 100 person-years, respectively (26 – 28). Lower seroconversion rates might have been expected in methadone programs, since methadone maintenance treatment effectively reduces and often eliminates heroin injection and thus should reduce virus transmission (1, 29). Crofts et al. (28) state that many of their methadone patients who seroconverted either had injected drugs while on methadone or had gaps in methadone treatment. Some early seroconverters were probably already infected with HCV at the time that they entered treatment. For others, the high prevalence and infectivity of HCV ensure that even occasional injection drug use can cause HCV infection. Other factors contributing to HCV seroconversion during methadone maintenance treatment include an inadequate methadone dose (30 – 32) and cocaine injection (14, 29).

Clinical Features

In two-thirds of patients, acute HCV infection is subclinical (33). Acute hepatitis C does not differ from other forms of acute hepatitis, but is very infrequent (33). Some cases escape attention because anti-HCV is not detectable in the early stages and HCV-RNA is the only marker (34). HCV infection becomes chronic in at least 85% of patients (33), and most of these patients seek medical attention because of abnormal liver tests which are accompanied by few, if any symptoms. In chronic HCV infection, serum aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) often fluctuate and may vary from normal to abnormal (35). Among HCV-infected patients who were current or former injection drug users who had been seen during at least four office visits, ALT was persistently normal in 42%, persistently elevated in 15%, and intermittently elevated in 43% (35). Repeated determinations of AST and ALT are needed for clinical assessment. Levels of ALT and AST are generally lower in chronic HCV infection than in other forms of viral and nonviral hepatitis, and they poorly predict liver histology (36). Liver biopsy is needed to assess the severity of liver injury. Liver histology was found to be less severe in HCV resulting from injection drug use than from transfusions (37). A few patients with chronic HCV develop cirrhosis rapidly, but most progress slowly or not at all. Cirrhosis has been seen in 20–30% after a follow-up of 10–20 years (33). The natural history of chronic HCV after 30–40 years, as in the person who acquires HCV from injection drug use in the late teens or early 20s and then remains otherwise healthy for decades, is as yet unknown.

The disposition of many drugs, especially those metabolized by oxidative pathways, is altered in chronic liver disease. Methadone undergoes oxidative biotransformation in the liver (38), but is also stored in the liver and released into the blood in unchanged form (39). This storage and release of unchanged methadone from the liver provides for low but stable plasma levels which maintain the patient in a stable state without opiate withdrawal or oversedation. Studies of methadone disposition in moderate (40) and severe (41) chronic liver disease revealed that most pharmacokinetic parameters for methadone were similar to those in controls. The essentially normal disposition of methadone in liver cirrhosis, even when severe, is attributed to a balance between damage to hepatic drug-metabolizing systems and damage to the storage and release functions of the liver regarding methadone (41). The usual methadone dose can be continued in patients with stable chronic liver disease, including advanced cirrhosis. In acute liver disease or acute decompensation of chronic liver disease, close clinical observation for signs of narcotic overdose or withdrawal is mandatory. A modest alteration in methadone dose may be indicated in some patients.

HCV infection is diagnosed by second- or third-generation enzyme immunoassay (42). Confirmatory testing is not necessary in chronic liver disease, but is important if serum aminotransferases are normal. Measurement of quantitative HCV-RNA level is needed prior to starting antiviral therapy for HCV, and to assess response, quantitative or qualitative HCV-RNA should be measured at the end of treatment and several months after treatment is stopped.

Alcohol and Hepatitis C

Patients with alcoholic liver disease have been found to have an increased frequency of anti-HCV (2, 43–45). The frequency of anti-HCV, confirmed by supplemental assays, in alcoholic liver disease ranges from 8–45%; it is seven times higher in alcoholics than it is in the general population (43). Injection drug use has been the most common risk factor identified in alcoholics with HCV infection (46, 47). In some studies, most of the alcohol users with anti-HCV had injection drug use or had had transfusions (45, 48). In others, however, parenteral risk factors were not found (45, 49, 50), and the high prevalence of anti-HCV in alcoholics was not explained (43). Lower socio-economic status may be a factor in the latter group (8, 43).

In our studies from 1978–1983, prior to the identification of HCV, liver cirrhosis was found to be significantly associated with alcoholism and injection drug use (51, 52). Cirrhosis was also diagnosed frequently in patients under age 35 with both alcoholism and injection drug use, but not with either one alone (51). We hypothesized that the observed frequency of cirrhosis was caused by additive and possibly synergistic effects of alcohol and one or more hepatitis viruses on the liver. When data from these patients were reanalyzed in the light of anti-HCV determinations on sera which had been frozen, cirrhosis was found in 30 of 67 injection drug users (45%) with anti-HCV and current or former alcohol abuse, but in only one of 19 (5%) with anti-HCV and no alcohol abuse (16).

Since the availability of anti-HCV testing, many studies have shown that patients with alcoholism and HCV infection have more severe liver disease than those with only one of these factors (43, 45). Advanced alcoholic liver disease has been reported at a younger age in subjects with HCV infection (46, 53). Habitual drinkers with HCV infection have been reported to have higher levels of HCV-RNA than non-habitual drinkers with HCV (54). In a recent study, weekly self-reported alcohol consumption in a group of predominantly low or moderate drinkers was highly correlated with serum HCV-RNA level and hepatic fibrosis (55). In another study, total lifetime alcohol consumption was found to be strongly associated with the presence of cirrhosis (56). Patients with cirrhosis were also found to have consumed more alcohol while HCV-infected than those without cirrhosis (56). Other reports have shown that patients with alcoholic liver disease and HCV have more severe liver histology (57, 58), progress more rapidly to cirrhosis (58), and have a higher mortality rate (57).

All of these data strongly suggest that alcohol consumption should be prohibited for patients with chronic HCV infection. Total abstinence is mandatory for HCV-infected individuals with current or former alcoholism problems, or those with cirrhosis or severe chronic hepatitis. Abstinence is also recommended for those with milder disease and no chemical dependency problems, since it is unknown whether there is any safe level of alcohol consumption for individuals with HCV infection.

Treatment

Standard antiviral therapy for chronic HCV infection consists of the combination of interferon alfa-2b given subcutaneously three times weekly and ribavirin given orally twice a day (59, 60). Sustained undetectability of HCV-RNA at 24 weeks after treatment with this regimen was seen in 38% of patients in an American study (59) and 43% in an international study (60); these results were significantly better than for those using interferon alone. In these studies, results of treatment with interferon and ribavirin were superior to treatment with interferon alone, even in the presence of factors associated with reduced response, such as genotype 1, low HCV-RNA level, and increased liver fibrosis. Both studies suggest that patients with genotype 1 are better when treated for 48 rather than 24 weeks. These findings suggest clinical utility for HCV genotyping. Patients who maintain normal ALT levels and undetectable HCV-RNA for six months after completing treatment are likely to remain in virologic remission (61) and not develop advanced cirrhosis (62).

Interferon side effects are generally tolerable, but serious depression and even suicides have occurred. Ribavirin causes reversible hemolytic anemia, which requires close monitoring. Both medications can cause numerous additional adverse reactions, with which treating physicians need to be familiar. Methadone maintenance patients tolerate interferon well, but data on ribavirin are not available yet.

Alcoholic patients (43) and patients with cirrhosis (63) had markedly reduced response rates to interferon alone, Further studies are needed to determine whether such patients have a reduced response to combined therapy with interferon and ribavirin. Preliminary data suggest that patients with cirrhosis will benefit most from a 48-week course of combination therapy (60).

Patients on methadone with end-stage cirrhosis have successfully undergone orthotopic liver transplantation. Transplant centers treating these patients should be familiar with appropriate pain management (2).

HCV-infected patients who subsequently acquire hepatitis A virus infection have a markedly increased risk of fulminant hepatic failure and death (64). Administration of hepatitis A vaccine to HCV patients who are susceptible to hepatitis A infection is therefore recommended.

Methadone-Related Issues

Methadone maintenance treatment has been used for the treatment of opiate addiction for more than 35 years and has proven to be safe even when administered for 15 years or longer (65). Methadone therapy is also associated with normalization of cellular immunity which had become abnormal during injection drug use (66). As already noted, methadone maintenance may be safely continued in the presence of stable chronic liver disease (40, 41). Therefore, it is appropriate to continue methadone maintenance treatment over years or decades, in patients with chronic HCV infection.

Injection drug users not infected with HCV, who enter a methadone program and do not use other drugs or alcohol, are very likely to remain HCV-negative. Expansion of methadone maintenance treatment would undoubtedly prevent some new cases of HCV infection. However, it is likely that the high seroprevalance of anti-HCV in injection drug users, coupled with the ability of HCV to be transmitted by small numbers of injections, will result in ongoing seroconversions to HCV, as suggested by the studies cited above (26–28). Further research in this area is needed. Methadone maintenance treatment should be available to any chronic injection drug user who desires this treatment (67, 68). Many studies have shown that higher doses of methadone lead to less ongoing heroin use during treatment and to greater treatment retention (30–32). Use of optimal doses of methadone should reduce the risk of seroconversion to HCV during treatment.

It is certain that methadone programs will contain large numbers of patients with all stages of HCV infection. Those with chronic hepatitis or early cirrhosis will need to be considered for antiviral therapy. Evaluating and treating large numbers of currently untreated patients will require considerable resources. Methadone maintenance programs should identify physicians in the community with an interest in treating HCV infection. It may be advantageous for some patients to receive hepatitis C treatment at the methadone clinic; a similar recommendation has already been made for antiretroviral therapy for HIV (69). It is reasonable to require methadone maintenance patients to abstain from alcohol and substance use before starting antiviral therapy, given the need for close clinical monitoring and the poor response seen in patients drinking alcohol (43). Also, patients with mild, stable, chronic HCV may do well with observation and no antiviral treatment (70).

New therapies, such as protease inhibitors, will probably become available in the 2000s. New antiviral agents will need to be assessed for interactions with methadone (38), as has now been reported for HIV protease inhibitors (71). Longer-acting interferon preparations administered once-weekly may be useful for patients who should not be given needles. Methadone maintenance patients with end-stage cirrhosis due to HCV should be considered for liver transplantation. Those who are not candidates for this procedure due to age, co-morbid medical conditions, poor social support, or ongoing alcohol or drug use will require supportive care.

In summary, HCV infection is one of many challenges which must be met in the process of providing quality medical care to methadone maintenance patients. Given the current incidence and prevalence data cited above, HCV infection is expected to remain a problem. Further research in the virology, epidemiology, treatment, and prevention of HCV infection is essential if better outcomes are to be achieved.

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Causes and Rates of Death among Methadone Maintenance Patients Before and After the Onset of the HIV/AIDS Epidemic

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Abstract

Causes of death and the mortality rates of active methadone patients and those who had left treatment were compared. Prior to the HIV epidemic, death rates among discharged methadone patients were more than twice that of patients who continued with their methadone treatment. However, the death rate from heroin-related causes in the post-treatment period was 51 times the rate among active patients. Alcohol-related conditions were the leading causes of death in patients more than 30 years old on methadone. During the post-treatment period, alcohol-related deaths were second to those of heroin-related causes. Alcohol-related deaths were particularly pronounced among black patients. Death rates among active male and female patients were identical, but the death rate for discharged female patients was greater than for discharged males

With the onset of the HIV epidemic in the 1980s, AIDS-related causes became the major cause of death in treatment. However, other causes of death, such as alcohol and other medical conditions, identified prior to the AIDS epidemic, persisted. AIDS-related deaths peaked in the mid-1990s and have recently subsided. However, within the past two years, deaths related to HCV have increased to 9% of all patient deaths in a major methadone program. With the emergence of HCV, deaths from this cause are expected to eclipse AIDS-related deaths within the next decade.

Key Words: Methadone maintenance, mortality rate, causes of death, HIV/AIDS

Outcomes of two cohorts of methadone maintenance (MM) patients, during and post-treatment, were described in detail in a seminal, NIDA-sponsored study by Dole and Joseph (1). The first cohort consisted of all patients admitted to MM treatment in New York City between 1966 – 1967 (n = 647), and the second, a stratified, random sample of 897 patients drawn from the roughly 17,000 admissions to MM treatment in New York City 1972. Outcomes were examined over a 10-year period, 1966 – 1976, and the findings showed superior patient functioning during maintenance treatment compared to the period after treatment. Twenty-five months after leaving treatment, 66% of patients who left in good standing relapsed to opiate and/or other drug abuse. Among patients discharged for cause, 98% relapsed to opiates and/or other drug abuse.

It was noted that alcoholism was the major medical problem during treatment and after discharge, affecting about 30% of all patients; and that complications of alcoholism were the leading causes of death among patients more than 30 years old. For patients under age 30, by contrast, the leading cause of death was violence. It was typically associated with relapse and exposure to the risks of illicit-drug-related activities.

In 1981, secondary analysis of these data focused on causes of death and death rates. The mortality data for the during and after treatment intervals were examined separately. The ten-year study period ending in 1976 is one which can safely be said to have preceded the HIV/AIDS epidemic, which began in earnest in 1981. The results were recorded in an internal report for the New York State Division of Substance Abuse Services (now, the Office of Alcoholism and Substance Abuse Services, OASAS) by Joseph et al. (2), but not published.

The present article is intended to rectify this omission by presenting the findings of the 1981

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report. In addition, we discuss selected results on mortality and MM treatment covering the HIV/AIDS era to the present, relying on data from Richman (3, 4) and Petry et al. (5). The intent is to explore changes in mortality, associated with HIV/AIDS among MM patients, during these two time periods.

Methods

Mortality During Treatment and After Discharge from Methadone Maintenance, Prior to the AIDS Epidemic: Findings from the Joseph, Appel, and Schmeidler (1981) Report

The objectives of the 1981 study were: (a) to compare during treatment and after discharge mortality rates for the 1544 patients in the two admission cohorts comprising the study; (b) to present the distribution of all categories of death for active and discharged patients; (c) to compare death rates among active and discharged patients to death rates in the general population; and (d) to describe selected characteristics of the patients who died.

All deaths which occurred during treatment were accounted for. However, it was not possible to account for all post-treatment deaths. Analytically, patient histories were classified into cycles of admission and discharge, and patients included in the project had as many as three such cycles during the study period. A number of patients known to have life-threatening conditions at discharge, such as active tuberculosis, cancer, alcoholism, and drug addiction, could not be located despite extensive record searches and contacts with family, friends, and acquaintances.

Since opiate addiction can mask symptoms of serious illness, it is likely that some patients at high risk of death did not seek treatment. Having "disappeared" from the streets, and not identified in institutional records, some of these former patients may have become part of the pool of "unidentifiable" deceased in the records of Bureaus of Vital Statistics in New York City and elsewhere.

As a result, the number of post-treatment deaths observed here must be considered a conservative estimate. As evidence for this, project staff were able to obtain information on four deaths from institutional records outside New York City, after extensive tracking by phone and letter. The possibility clearly exists that other former patients died outside New York City after discharge.

Causes of death were classified as follows: (a) drug-related, (b) violence, (c) accident, (d) medical, and (e) unknown. The causation category "drug-related" was subdivided into opiate-only, opiate with alcohol, opiate with non-opiate drugs, non-opiate-only, and alcohol-only. Cause-of-death information was developed from reasons indicated on official death certificates, from autopsy reports, and from other relevant sources, including medical and clinical data from patients' programs. Descriptions of causes of death such as "alcohol only" is for ease of communication — actual causes could be cirrhosis and alcoholic hepatitis, among others, which may be traceable to chronic alcoholism.

Finally, mortality rates were constructed by tabulating the number of deaths of a given type in relation to the amount of time that the individuals involved were in a given status, i.e., in treatment or out of treatment. Thus, mortality rates are specified as rates per 1,000 person-years for each status.

Results

Among the 1,544 patients studied, there were 176 deaths from all causes during the 10-year study period of 1966-1976. Deaths were verified through hospital and treatment program records, social security records, records of the Bureaus of Vital Statistics in New York City and other localities, prison records, newspaper accounts, records of the New York City Medical Examiner's Office, and family records.

The results, presented in Table 1, show the numbers of deaths and death rates during treatment and after discharge, for the various causes of death, including the five subclasses of "drug-related." Overall, there were 93 deaths during treatment and 83 deaths after leaving treatment. Converted to rates reflecting differences in time spent in treatment compared to out of treatment, the post-treatment death rate of 35.2 (per thousand person-years) was more than double the rate of 15.2 during treatment.

An even greater divergence was observed for the results pertaining to drug-related deaths. There were 37 during-treatment and 56 after leaving treatment. The findings for opiate-related deaths were especially striking: there were only 2 such deaths during treatment and 36 after treatment. One of the two deaths during treatment was of a patient under treatment for only three days; the second death was of a noncompliant patient who reported to the clinic only intermittently. Neither patient was pharmacologically stable. These values convert to death rates of 15.3 post-treatment and 0.3 during-treatment. The post-treatment death rate where the cause was opiate-related was thus 51 times as large as the during-treatment rate.

The data on deaths classified as alcohol-related are also shown in Table 1. Many more of the during-treatment cohort died of alcohol-related causes than did the post-treatment group, although the adjusted rate in the latter group was slightly higher (7.2/1000 person-years vs. 5.1/1000 person-years). A similar pattern of higher during-treatment death rates compared to post-treatment death rates was found for the deaths related to medical causes, 4.2, versus 2.6 respectively.

Another way of characterizing the data is to compare the several categories of causation during treatment and after treatment in terms of relative contribution to the overall death rate. For during-treatment deaths, for example, 39.5% of the overall rate is accounted for by drug-related causes, mainly alcohol; 30.5% by medical causes; and 30.5% by the remaining categories combined (i.e., violence, accidents, and "unknown"). For post-treatment deaths, however, over two thirds of the (higher) overall death rate, 67.4%, is attributable to drug-related causes; 7.1%, to medical causes; and 25.5%, to the several other causes. In other words, drugs of all kinds play a substantially more important role in post-treatment mortality than they do for during-treatment mortality.

Mortality data were obtained from the NYC Department of Health for the population living in the following areas: Central Harlem, East Harlem, Morrisania, Mott-Haven, Bedford-Stuyvesant, Brownsville, Fort Greene, Williamsburg-Greenhaven, and Jamaica-East. Death rates for these nine areas were combined for the years 1974, 1975, and 1976, and averaged. Separate rates were computed for the age groups 18 – 24, 25 – 44, and 45 – 64. Death rates for the same age ranges were computed for the follow-up study subjects, one set for the during-treatment period and another for the post-treatment period.

The results are presented in Table 2. The death rates of patients are higher than those for the general population. The biggest difference in rates was found for the 25 – 44 age group. The rate for the general population involved the number of deaths per 1000 population per year; the rate for patients, on the other hand, involved the number of deaths relative to the cumulative years of all patients in treatment (or after treatment) adjusted to a base of 1000 patient years.

Selected features of patient addiction histories are presented in Tables 3 and 4. Table 3 shows that, compared to patients who were alive at follow-up, patients who died started using heroin somewhat later, had addiction histories that were 2 – 4 years longer, and first entered treatment when 4 – 6 years older. However, the average age

TABLE 1
Numbers of Deaths and Death Rates by Treatment Status and Cause of Death

Cause of Death	n	During-Maintenance Rate per 1000 Person-Years	n	Post-Maintenance Rate per 1000 Person-Years
Drug-Related	37	6.0	56	24.0
Total Opiates	2	0.3	36	15.3
Opiates only	2	0.3	19	8.1
With Alcohol	0	0	15	6.4
With nonopiates	0	0	2	0.9
Alcohol	31	5.1	17	7.2
Nonopiates	4	0.7	3	1.3
Violence	15	2.5	14	6.0
Accident	5	0.8	1	0.4
Unknown	8	1.3	6	2.6
Medical	28	4.6	6	2.6
Total	93	15.2	83	35.2

TABLE 2

Patient Deaths and Rates for Various Age Groups by Treatment Status and Compared to Selected New York City Death Rates in 1974, 1975 and 1976

Age Group	n	During-Maintenance Rate per 1000 Person-Years	n	Post-Maintenance Rate per 1000 Person-Years	Average Selected N.Y.C. Rates*
18–24	6	8.3	4	10.8	1.6**
25–44	74	15.7	68	38.6	3.3
45–64	13	18.9	11	58.4	11.6

* Death rates among the general population were obtained from the New York City Department of Health for the following areas: Central Harlem, East Harlem, Morrisania, Mott Haven, Bedford-Stuyvesant, Brownsville, Fort Green, Williamsburg-Greenhaven, and Jamaica-East. Rates for the years 1974, 1975, and 1976 were combined and averaged.

** The average selected N.Y.C. rates depend on number of deaths per year per 1000 population in an area using 1970 census data. While similar to the rates developed for patients (rates per 1000 person-years at risk) the two rates are not completely comparable.

TABLE 3

Addiction History and Treatment Characteristics for Various Categories of Follow-up Subjects

	Characteristics				
Patient Category	Years (Mean ± SD) Age of First Heroin Use	Years (Duration ± SD) of Addiction	Years (Mean ± SD) Age When First Entered Methadone Treatment	Months (Duration ± SD) of Methadone Treatment	Months (Duration ± SD) of Post-Maintenance Observation
Died in Treatment n = 93	20.1 ± 5	14 ± 7	34 ± 8	41 ± 33	6 ± 15
Died After Treatment n = 83	19.5 ± 5	14 ± 6	34 ± 7	24 ± 23	26 ± 24
Continuously Active n = 511	18.7 ± 4	12 ± 7	30 ± 8	76 ± 35	—
Discontinuously Active n = 262	18.7 ± 5	11 ± 7	29 ± 7	49 ± 32	22 ± 20
Discharged n = 594	18.9 ± 4	10 ± 7	28 ± 7	27 ± 29	33 ± 23

TABLE 4

Numbers of Deaths and Death Rates by Treatment Status, Sex and Ethnicity

	n	During-Maintenance Rate per 1000 Person-Years	n	Post-Maintenance Rate per 1000 Person-Years
Sex				
Male	77	15.0	65	33.0
Female	16	15.0	18	45.0
Ethnicity				
Black	48	19.0	52	47.0
White	27	12.0	18	26.0
Hispanic	18	15.0	13	25.0
Total*	93	15.2	83	35.2

*Total is for sex or ethnicity

at death among patients who died was essentially the same for those who died during and after treatment, 38.5 and 38.1 years of age respectively.

Table 4 shows the sex and ethnic backgrounds of patients who died during treatment and after discharge. Consistent with the roughly 3-to-1 ratio of males to females in MM treatment, more males than females died during treatment and after discharge. However, male and female death rates were identical during treatment. After discharge, the female death rate was higher than the male death rate.

The death rate for blacks was slightly higher than the rates for whites and Hispanics. In the post-treatment group, however, whites and Hispanics had nearly the same rate, while the rate for blacks was nearly double that of the latter groups. As shown in Table 5, alcohol-related conditions were a major cause of death among blacks, both during and especially after treatment. Sixty-one percent (61%) of the alcohol-related deaths occurred among blacks in the during-treatment group. In the post-treatment period, 91% of these deaths occurred among blacks. It is important to note that for combined during- and post-treatment groups, 71% of the patients had a known moderate-to-severe recorded alcohol problem before admission (6).

As shown in Table 6, the death rate during the month after admission is more than double the overall during-treatment death rate. Similarly, the death rate in the first month after discharge is more than double the overall post-treatment death rate.

Discussion

These findings on mortality among patients during, roughly, the first decade of experience with MMT in New York City are encouraging and disturbing at the same time. The retrospective analysis of an observational study without controls, produced remarkably similar results to those in the study by Gronbladh et al. in which randomized and waiting list controls were included (7).

The results are disturbing on a number of counts, not the least of which is the high rate of mortality associated with alcoholism, especially among black patients. In 1997, the New York State Office of Alcoholism and Substance Abuse Services was able to offer alcoholism treatment for methadone maintenance patients within the state's own treatment facilities, after educating the staff about methadone maintenance.

Mortality among Methadone Maintenance Patients After Onset of the HIV/AIDS Epidemic

The question arises as to how mortality has changed among MM patients, active as well as discharged, since the onset of the HIV/AIDS epidemic in the early 1980s. One of the most dramatic and well-documented changes has been the overall increase in mortality among active methadone patients brought about by AIDS (3). In the report just cited, mortality data were developed and compiled for all clinics of the Beth Israel Medical Center's (BIMC) Methadone Maintenance Treatment Program (MMTP) in New York City, beginning in 1977, with findings through 1986, and preliminary 1987 results.

The mortality rate used was the percentage of patients in treatment during a given year who died in that year. Numbers of patients treated annually between 1981 and 1986 varied from a low of 8,347 in 1983 to a high of 9,011 in 1986. The mortality rate remained stable at 1% between 1977 and 1980, and was also 1% for 1981, the first year of the AIDS epidemic. In each year

TABLE 5

Numbers of Alcohol Deaths and Alcohol Death Rates by Treatment Status and Ethnicity

Ethnicity	n	During-Maintenance* Rate per 1000 Person-Years	n	Post-Maintenance* Rate per 1000 Person-Years
Black	19	7.6	29	26.0
White	5	2.2	1	1.5
Hispanic	7	5.7	2	3.8
Total	31	5.1	32	13.6

*Seventy-one percent of patients who died from alcohol related diseases had records of drinking problems before admission to methadone maintenance treatment.

Alcohol history prior to entering treatment of the remaining 29% could not be located.

TABLE 6

Number of Deaths and Death Rates by Time in Treatment and by Time After Treatment

Interval — (Months)		Number of Deaths	Years at Risk	Death Rate
		During Treatment		
0.1	1	7	171.4	40.8
1.1	3	4	320.3	12.5
3.1	6	6	430.0	14.0
6.1	9	10	383.0	26.0
9.1	12	4	348.0	11.0
12.1	12	11	1133.0	9.7
24.1	24	8	916.0	8.7
36.1	48	12	650.0	18.5
48.1	60	7	445.3	15.7
60.1		24	1332.0	18.0
Total		93	6130.0	15.2
		After Treatment		
0.1	1	9	100.0	90.0
1.1	3	6	184.0	33.0
3.1	6	7	250.0	28.0
6.1	9	10	224.0	45.0
9.1	12	4	204.0	20.0
12.1	24	23	620.0	37.0
24.1	36	5	365.0	14.0
36.1	48	7	195.0	36.0
48.1	60	5	99.0	51.0
60.1		7	114.0	61.0
Total		83	2355.0	35.2

thereafter, the mortality rate increased, reaching 2.5% in 1985 and in 1986; from available results at the time of the report, the rate was projected to increase further to 3.3% for 1987. The impact of AIDS on patient mortality was demonstrated by data on AIDS-related deaths relative to all deaths in 1982 and in 1986. The AIDS-related mortality rate was 4.3% in 1982 and 39.5% in 1986, with the total number of deaths having more than doubled from 122 in 1982 to 236 in 1986.

Interestingly, as Richman's findings demonstrate (3), the absolute numbers of patients dying from other causes, e.g., chronic liver disease related to alcohol, violence, acute infectious diseases, were similar in 1982 and 1986, though the rate of drug-related deaths nearly doubled from 5.4% in 1982 (6 of 112) to 10.2% in 1986 (24 of 236). In short, while some of the causes of mortality prior to AIDS continued to be prevalent, the increased mortality among MM patients in 1986 compared to 1982 was caused largely by AIDS. Joseph and Springer (8), using a wider variety of data sources for the period of mid-1985 through mid-1987, reached a similar conclusion.

Another extensive study of mortality among MM patients was undertaken by Petry et al. (5). It covered deaths occurring in another New York City MMTP, this one administered by the Albert Einstein College of Medicine (AECOM). It covered the years from 1975 through 1986, thus also capturing the early years of the AIDS epidemic. Causes of death were classified as AIDS, trauma (accident, violence, non-drug-induced suicide), drug overdose, alcohol-related, and medical. The data show large increases in the number of deaths in 1986 compared to 1981 — over 70 compared to about 20, with the bulk of the increase attributable to AIDS and medical causes, and a small increase in alcohol-related deaths. Interestingly, a closer examination of Richman's 1987 mortality data (3) for eight categories of medical conditions, e.g., endocarditis, heart disease, malignancy, cerebral hemorrhage, renal disease, non-alcohol liver disease, etc., showed increases for six of the eight categories, consistent with the findings by Petry et al. for medical causes (5). Trauma and drug overdose causes, on the other hand, showed a slight decline.

The mortality assessment project undertaken by Richman and colleagues for the BIMC MMTP has continued through the present. Some preliminary findings indicate that the AIDS-related mortality rate among MM patients increased each year from 1987 and peaked in 1995 — the rate in that year was over 65%. The rate has declined significantly in the past four years to about 29%. However, in the second year of the HIV/AIDS epidemic, 1982, the rate was 4.3%. So even very recently, AIDS-related mortality among active MM patients in the BIMC system was nearly seven times its rate very early in the epidemic.

Causes of death and AIDS-related mortality among discharged MM patients appear to be less well-documented. A recent meta-analysis of studies on the risk of death in and out of methadone maintenance treatment (9) found that heroin addicts were about one-fourth as likely to die while receiving methadone maintenance as they were when not in MM treatment. The specific impact of MM seemed to reside in its ability to reduce the risk of heroin overdose or suicide. Apparently unaware of the Richman report (4), the authors also speculate that the relative risk of death during maintenance has probably increased considerably because of AIDS-related mortality.

The analysis did not address the issue of mortality among former MM patients as distinguished from treatment-naive heroin addicts, which was partially addressed in a Swedish study by Gronbladh et al. (9). The latter study covered both voluntary discharges from MM in good standing and discharges for cause. The yearly death rate for the patients discharged in good standing, 1.65, was very comparable to the rate for active patients, 1.4, though in terms of causes, none of the active MM patients died of heroin overdose, while 50% of voluntary discharges (3/6) and 61.5% of involuntary discharges (16/26) died for this reason. No deaths related to AIDS were reported in the Gronbladh study.

Another focus of the BIMC death-monitoring project has been to identify nonalcoholic liver disease as a cause of death among MM patients. Some deaths in this category have been due to hepatitis B, but clearly, the rate for nonalcoholic liver disease overall has been increasing due largely to hepatitis C. With the identification of the virus and the recent availability of an antibody test for it (10), the BIMC death monitoring project has started reporting hepatitis C deaths separately. In 1999, hepatitis C was the cause of 9% of all patient deaths; along with unspecified liver disease, nonalcoholic liver disease represented 11% of total deaths. The number of hepatitis C deaths in 1998 was the same as in 1999, though total deaths were fewer. Thus, the pattern of mortality among active MM patients is shifting again: HIV/AIDS has declined (due partly to antiretroviral therapy) and hepatitis C has increased. In view of the long incubation period for hepatitis C sequelae, mortality associated with them may soon eclipse mortality from AIDS.

This article was intended mainly to present findings on mortality for methadone maintenance patients both during and after treatment, findings from the Dole-Joseph follow-up study (1) which covered the 10-year period 1966 – 1976. Secondly, we wished to present selected findings on the same issues since the onset of the HIV/AIDS epidemic in 1981, to begin addressing how the numbers and kinds of deaths among patients had changed and in what respects they were continuous with the pre-AIDS era.

The mortality findings from the Dole-Joseph study are unequivocal in showing a higher overall mortality rate after discharge compared to during treatment, and an extremely high opiate-related rate after as compared to during treatment, a 51-fold difference. This difference helps confirm the efficacy of methadone maintenance treatment in reducing the opiate-related death rate. However, we had very little data on possible differences between patients who died during treatment compared to those who died after treatment aside from their receipt of MMT. We did find there was no difference in average age for patients who died during and those who died after treatment. Since narcotics use can mask symptoms of serious illness, which by the time of admission may be at advanced stages, the opportunity to receive medical care following admission may be to no avail for vulnerable patients. This would help explain the higher death rate related to medical causes during treatment compared to after treatment. Other findings of note concerned the powerful role of alcohol-related causes of death both during and after treatment, and the disproportionate vulnerability of black patients in this respect. The majority of alcoholic patients were clinically compliant and died during treatment; the smaller percentage of alcoholic patients who presented behavior problems were discharged and died after treatment. Also of interest is that male and female death rates were identical during treatment while the female death rate after treatment was higher than the rate for males, contrary to what is found in the general population in the same age range.

The findings of Richman (3, 4) and Petry et al. (5) were reviewed to begin examining how the AIDS epidemic affected the numbers and kinds of mortality among active and discharged MM patients. Even though these two sources covered the earliest period of the epidemic, from 1981 to 1986, it became clear that AIDS had become the dominant cause of death after 1983 (preliminary unpublished data). The findings of Petry et al. (5) showed that medical causes of death increased, and to a lesser extent, alcohol-related causes. Richman's results indicate that the number of deaths due to causes identified prior to the AIDS period remained relatively stable after the onset of the AIDS epidemic in 1983. In addition, she reported a large increase in drug-related causes.

The meta-analysis of mortality studies among active and discharged patients and untreated addict controls by Caplehorn et al. (9) makes clear that this area needs more systematic investigation. Samples of decedents have been small, categories of causes of death, variable, and ways of computing mortality rates among patients and among general population comparison samples, also variable. The differential survival of active MM patients compared to discharged patients and untreated heroin addicts is a consistent finding from the limited data available. Systematic, objective data on mortality among MM patients is essential for supporting expansion of treatment capacity to enhance treatment outcomes, and also to curtail HIV/AIDS transmission among injection drug users. Emblematic of the dynamic nature of causes of mortality among MM patients are the very preliminary data on deaths from hepatitis C (10). Along with the decline in AIDS-related deaths, they suggest that a major shift in the pattern of MM patient mortality is underway.

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The Converging Epidemics of Mood-Altering-Drug Use, HIV, HCV, and Partner Violence:

A Conundrum for Methadone Maintenance Treatment

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Abstract

Background: Accumulating evidence suggests that partner violence may be associated with HIV risk behavior and drug use among women in methadone maintenance treatment programs (MMTPs), yet the mechanisms linking these overlapping problems remain unclear. The main purpose of this qualitative study is to explore in detail how drug-related activities and HIV risk behavior occur in the context of a recent episode of partner violence among women in MMTPs.
Methods: We conducted and analyzed in-depth interviews with 31 women who reported having experienced physical or sexual violence by an intimate partner during the past year. Guided by existing research, feminist theory and trauma theory, we constructed a set of questions which were designed to explore multiple ways in which drug-related activities or HIV risk behavior may be linked directly or indirectly to the recent event. To examine the extent and significance of the woman's and/or her partner's drug-related activities or sexual HIV risk issues occurring immediately before, during and/or after the most recent event, we adapted a series of techniques for thematic analysis of qualitative data.
Results: Of the 31 women who reported recent events: 83.8 % (n=26) recalled recent events in which there was some drug-involvement; 40% (n=13) indicated that both she and her partner were involved in drug-related activities during the most recent event of partner abuse; 35% (n=11) reported that the partner was drug-involved; and only two women (6.4%) indicated that they alone had been drug-involved. One-fifth (19.3%, n=6) of the women indicated that they had used drugs immediately after the event because they were upset or in physical pain. One-fifth of the women (n=6) reported that they had coerced, unprotected sex during or after the most recent incident.
Conclusions: The multiple ways in which the use of mood-altering drugs are related to partner violence and the occurrence of coerced, unprotected sex underscore the need to design specific interventions for preventing drug relapse, and HIV and HCV infection among abused women in MMTPs. Treatment and policy implications of study findings are discussed.
Key Words: Domestic violence, methadone, HIV prevention, hepatitis C, drug use, sexual risk behavior.

Introduction

Over the last decade, emerging evidence has implicated partner violence as a risk factor for drug use and HIV risk behavior. Estimated lifetime rates of partner violence reported by drug-involved women range from 60–75% (1–3). These rates are two to three times higher than the 21–34% range found in national surveys of general populations of women (4). Accumulating evidence has also linked the epidemics of partner violence and sexually transmitted diseases (STDs), including human immunodeficiency virus (HIV) (5–12). Recent research has also indicated that partner violence and STDs are associated among women in Methadone Maintenance Treatment Programs (MMTPs) (13, 14). The relationship between partner violence and hepatitis C (HCV) has yet to be researched. HCV is most commonly transmitted through multi-person use ("sharing") of drug injection equipment by drug users (15), however, it may also be sexually transmitted if a person has genital sores or sexually transmitted diseases where a possibility of blood transfer exists.

Although the literature suggests that partner violence, HIV and drug use are converging epidemics, particularly among low-income, urban women, the mechanisms linking partner violence to drug use and risk behavior for HIV and HCV remain unclear. This lack of clarity has led researchers to recommend the need for fine-grained contextual data on the mediating role of drugs and HIV risk behavior in victimization experiences (6, 16–18). Understanding how

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Some of this information was presented at the American Public Health Association, 127th annual meeting, Chicago, IL (1999).

partner violence contributes to drug relapse, and HCV and HIV infection, may provide further information to aid in the design of more contextually specific interventions in MMTPs.

Existing research on the relationship between drug use and partner violence indicates that the relationship is complex, varying by type and severity of drug use as well as by whether the perpetrator, the victim or both are drug-involved (19, 20). Over the last two decades, numerous studies have documented associations between alcohol use by males and violent behavior toward their intimate partners (19, 21, 22), and associations between male drug use, particularly crack/cocaine and marijuana use, and partner violence (23). Substantial research also suggests that a woman's alcohol use increases her risk of being abused by a partner (24–27). More recent findings suggest a relationship between a woman's drug use and abuse by a partner (3, 28–31).

Goldstein's tripartite model (32) linking drug use and violence lends further insight into this complex relationship, suggesting that psychopharmacological, economic compulsive, and systemic effects of drugs should be considered as factors contributing to violence. The more traditional psychopharmacological explanation posits that substance use acts to disinhibit violent behavior. More recent research has focused on how substance use induces cognitive disruption, which impairs the individual's ability to process social interactions (33). Other researchers, however, have argued that drug use is an instrument of domination and control used to excuse the exercise of violence against intimates (34, 35).

Economic compulsive violence occurs when the drug user engages in violent crimes to support costly drug use or when violence erupts as a result of conflict over procuring drugs (32). Economic compulsive violence may emerge in intimate relationships when drug users fail to supply their intimate partners with drugs, when they argue about spending money on drugs, or when they steal drugs or money from each other. Systemic violence refers to the patterns of social interactions within the system of drug distribution and use that are predisposed to violence (32). Systemic violence may erupt in intimate relationships in the form of disputes over splitting drugs.

Similarly, research on the relationship between partner violence and HIV indicates multiple, bi-directional linkages. Studies have found that compared to non-abused women, abused women are less likely to report using condoms (11, 13); they are more likely to report partner-related risk behaviors — e.g., having sex with an injecting drug user (IDU), an HIV-infected partner, or a partner who has had sex with more than one partner (6, 13, 36) — and more likely to report having more than one partner themselves or exchanging sex for money (6, 13). Recent research conversely suggests that disclosure of positive HIV serostatus was associated with specific incidents of partner violence among a nationally representative probability sample of 2,864 HIV-infected women (12).

Qualitative research may further explain the multi-dimensional, bi-directional associations which have been found between partner violence, drug use, and HIV, and provide information so that intervention strategies can be made that are more effective in reducing drug relapse, and both HIV and HCV risk among abused women in drug treatment. The purpose of this study was to: (a) briefly describe background characteristics, current drug use, and sexual and physical partner violence as measured by the Revised Conflict Tactics Scale (37) and sexual and drug-related risk behavior; (b) elicit detailed information on different contexts in which drug-related activities and HIV risk behavior occurred immediately prior to, during or after a recent episode of partner violence among a sample of 31 abused women in MMTPs, using data from in-depth narrative interviews; (c) provide detailed recent event analysis using three case examples; and (d) discuss implications of study findings with respect to policy and practice at MMTPs.

Methods

Recruitment and Eligibility

Data were drawn from a National Institute on Drug Abuse (NIDA) funded study to examine the relationships between HIV-risk behavior, drug abuse and intimate-partner violence in women enrolled in MMTPs. This study had two phases: a qualitative phase, consisting of focus groups and in-depth interviews; and a longitudinal quantitative phase. Women were recruited from three MMTPs in New York City. Between May and December 1997, twenty-minute structured, face-to-face interviews were conducted with 251 women for screening purposes to determine whether they met eligibility criteria for the qualitative phase of the study.

To be eligible, women needed to report that they were between the ages of 18 and 55; had been on methadone for at least three months; had an intimate sexual partner in the past year; and had experienced physical or sexual abuse by someone who they considered to be a boyfriend, spouse, father of their children or ex-spouse. Of these eligible women, 68 women participated in focus groups. A subsample of 38 women from the focus groups was selected randomly to participate in in-depth narrative interviews. Data for the present study were drawn from 31 women who had completed data on a recent event of partner violence.

Trained female research assistants conducted interviews in private rooms on-site at the methadone clinic. The interview lasted about two hours. During the first 15 minutes, we read a consent form to the participants which detailed the purpose of the study, confidentiality procedures and their rights as research participants, and then asked the participants to sign the form. The institutional review board of the participating methadone maintenance treatment program approved the protocol for this study. The last 15 minutes of the interview were reserved as a debriefing period. During this time, we assessed the needs and made referrals for women who exhibited signs of distress during the interview or who expressed a need for help. We presented the women with a handbook of services in their community (e.g., housing, domestic violence services, job training, counseling, and gynecological care) and encouraged them to call us if they needed further help with referrals. At the end of the interview, participants were paid $20 as compensation.

Data Collection

In order to ensure that the interviewers did not overly influence or construct respondents' accounts of their experiences and beliefs, interviewers allowed the participants' responses to direct the flow of the interview — using active probes to keep the interview on target (38).

The interview protocol consisted of two parts. The first portion of the interview covered a range of topics designed to illuminate aspects of the personal biographies of the respondents and their intimate sexual partners, their histories of victimization, substance use and HIV-risk behavior, the history and nature of their intimate relationship, and the nature of their interpersonal relationships in general. We did not ask questions about HCV risk behavior apart from HIV risk behavior. In the second portion of the in-depth interview, each respondent was asked to reconstruct the interactions that occurred within her most recent event of partner abuse. After a respondent was given the opportunity to recount the event in her own words, the interviewer used a series of probes to elicit details regarding key transitional moments of the interaction described. Several scholars have focused on violent event data in their research because of the analytic advantages that the approach affords (39–41). We chose this approach because it allows us to capture detailed descriptions of the contexts in which partner violence occurs. In addition, this event data helps us to understand the specific processes involved in violence, HIV risk and drug-related behaviors under study.

Our inquiry into these recent events of partner violence was influenced by existing research cited in the above sources, as well as by feminist theory and trauma theory. Feminist theory holds that an imbalance of power and control between women and men in intimate relationships may increase the risk of partner violence and unsafe behaviors that put women at risk for HIV (42–44). Feminist theory also claims gender discrepancies in power and control over procuring, sharing and using drugs. Drug-related activities and HIV risk behaviors take place within a wider context of culturally based gender role expectations and structural forces, such as poverty and racism (45). Gender power differentials are intensified even further for women in abusive relationships (11). Viewed within this theoretical framework, intimate violence in drug-related or HIV risk-related contexts occurs as an extension of the unequal distribution of power, social status, and labor between men and women (42, 46–48). Because drug-dependent women often engage in illicit activities including those that symbolize sexual availability, they are perceived as violating traditional gender role norms and are consequently regarded as "low status" women (20, 24, 48). Their low social status further enables intimate partners to exercise control and power in all aspects of the relationship, including determining when, where and how drug use and unprotected sex will occur, and initiating unprotected sex.

Alternatively, trauma-based theory and research suggest that when women become involved in drug-related activities, they are more likely to be exposed to partner violence and traumas of all kinds, thereby increasing their risk of post-traumatic stress and future substance abuse as a self-medicating response to the emotional and physical pain of the violent traumas. Accumulating evidence has linked substance abuse to post-traumatic, stress-related events of all kinds, including partner violence (16, 49–51). Trauma theory suggests that the numbing and desensitizing effects of traumatic experiences like partner violence may enhance the likelihood of women engaging in a wide range of risky behaviors, including having unprotected sex with risky partners (52, 53). The consequences of not pursuing protection with a partner may loom small for a woman who has experienced multiple traumas.

Guided by existing research, feminist theory and trauma theory, we constructed a set of questions with respect to the recent event, which were designed to explore: (a) the extent to which drug-related activities (i.e., procuring, sharing and using drugs) of the woman and/or her partner occurred before, during or immediately after the violent event; (b) the participant's perception as to the significance of these drug-related activities in triggering or escalating the violent event; (c) the extent to which HIV risk issues (i.e., request for condom use, disclosure of STDs, refusal to use condoms, insistence on sharing needles) occurred immediately prior to the event and the participant's perception of how significant a role the issue played in triggering or escalating the violence; and (d) the extent to which the event itself involved HIV risk behavior (i.e., forced or unwanted, unprotected sex, injecting drug use). Feminist theory also guided our questions about situations in which the low social status of drug-involved women and negative stigma associated with their drug and alcohol use may have served as a pretext for their partners' emotional and physical abuse. Trauma theory informed our inquiry about situations in which women used drugs or alcohol to recover from the physical or emotional pain after an abusive episode. We differentiated patterns of violence by type of drug (i.e., heroin, crack/cocaine, and alcohol) and by whether the woman, her partner or both were involved in or abstaining from drug-related activities.

Study Limitations

Material presented here is meant to be suggestive. Sampling procedures and number of participants are insufficient to render data that may be generalizable. Further, several factors may have influenced the ability of women to recall and disclose specific details about the event. First, the time frame in which the experiences of abuse and drug use were recounted varied considerably, as some women discussed past relationships, some current long-term relationships, and some relationships that had started relatively recently. This variation in time frames may have differentially affected the ability of the women to recall. Second, several women reported that they had been high during the event, which may have further affected their recollection of the event. Finally, some women may have been reluctant to disclose their drug use or HIV risk behaviors to interviewers, due to social desirability reasons or fear of jeopardizing their status in the MMTP. In order to lessen the bias that might be derived from the perception that research staff were "clinic insiders," we, as interviewers, were careful to establish that the study had no connection with the operation of the methadone clinic and that, as researchers, we followed strict confidentiality procedures.

Data Analysis

Each interview was audiotaped and transcribed verbatim. Interview data were coded using a modification of the methods developed by several researchers (54–56). The following steps were taken. First, all the interviews were summarized to develop an overview of the data. Second, based on these summaries, a list of the topical areas represented in the data was composed. Segments of the transcripts were coded under these topic headings using NuDist (Non-numerical Unstructured Data Indexing, Searching and Theorizing) software.

Then, in order to examine the extent and significance of the woman's and/or her partner's drug-related activities or HIV risk issues occurring immediately before, during and/or after the most recent event of violence, we adapted a series of techniques developed by Boyatzis (56) for thematic analysis of qualitative data. According to Boyatzis, "thematic analysis enables scholars, observers, or practitioners to use a wide variety of types of information in a systematic manner that increases their accuracy or sensitivity in understanding and interpreting observations about people, events [and] situations." We compared themes that we had identified from a close reading of cases within each subsample. Themes consist of generalized statements by respondents about experiences, behavior, beliefs, attitudes, values, or sentiments (55, 56). Lists of emerging themes were also compared across subsamples at intervals during the analysis. Finally, the themes generated from each subsample were compared for all the cases. In addition to this event analysis among the 31 participants, we selected three case studies which are representative of some of the general themes that emerged from the data regarding how drug-related activities and HIV risk behavior evolve and play out in tandem with partner violence. In these case studies, names have been substituted and any personal identifying information has been removed to protect the confidentiality of the participants.

Results

Socio-demographic Background

As shown in Table 1, the majority of participants were Latina (51.6%) and African-American (29.0%). The average age of the participants was 37. Fewer than one-third (29.0 %) were married or had common-law relationships, but three-quarters of the women (74.0%) had children under the age of 18. Only two women (6.5%) were currently employed. More than three-quarters (77.4%) of the women reported that they hadn't had enough money to buy food in the past year and one-quarter (25.8%) indicated that they had been homeless in the past year.

Partner Violence

The vast majority of the sample (87.0%) reported experiencing a minor physical assault from an intimate partner in the past year, based on the Revised Conflict Tactics Scale, and more than half (58.0%) indicated that they had experienced a severe physical assault in the past year (Table 2). Almost two-thirds (64.5%) reported experiencing a minor sexual coercion from an intimate partner in the past year and 12.9% indicated severe sexual coercion. One-third (32.3%) reported experiencing severe physical injury from an intimate partner in the past year.

Drug Use and HIV and HCV Risk

Almost one-third (29.0%) had used heroin in the past 90 days and 41.9% had used crack/cocaine (Table 3). More than one-third (35.4%) reported drinking alcohol one or more times per week. One-fifth (19.4%) indicated that they had injected drugs in the past year. Nearly two-thirds (61.2%) reported that their partner had a substance abuse problem. Three-quarters (74.1%) reported having had sex in the past 90 days. Sixty percent (60%) had never used a con-

TABLE 1

Background Characteristics of Participants (n=31)

Age — in years	37.8 ± 6.15	
Ethnicity	(n)	(%)
African-American	9	29.0
Latina	16	51.6
White	5	16.1
Other	1	3.2
Marital Status		
Single	22	70.9
Married or common-law	9	29.1
Have children under age of 18	23	74.2
Less than high school education	16	51.6
Currently employed	2	6.5
Homeless in the past year	8	25.8
Not enough money to buy food in past year	24	77.4

TABLE 2

Prevalence of Partner Violence in the Past Year as Measured by Revised Conflicts Tactics Scale

(n=31)

Revised Conflict Tactics Subscale	n	%
Minor physical assault	27	87.0
Severe physical assault	18	58.0
Minor Sexual Coercion	20	64.5
Severe Sexual Coercion	4	12.9
Minor Injury	14	35.1
Severe Injury	10	32.3

TABLE 3

Drug Use and HIV Risk Characteristics of Participants

(n=31)

Characteristic	n	%
Heroin use in the past 90 days	9	29.0
Crack/cocaine use in the past 90 days	13	41.9
Alcohol use one or more times a week in the past 90 days	11	35.4
Injecting drugs in the past year	6	19.4
Partner has a substance abuse problem	19	61.2
Had sex in the past 90 days	23	74.1
Never used condoms during sex in the past 90 days	14	60.0
Exchanged sex for money/drugs in the past 90 days	6	19.4
Had sex with >1 partner in the past 90 days	6	19.4
Had sex with an HIV+ partner in the past 90 days	5	16.1

dom with their main intimate partner. One-fifth (19.4%) indicated that they had exchanged sex for money or drugs during the past 90 days. Another one-fifth (19.4%) indicated that they had had sex with more than one partner in the past 90 days, and 16.1% reported having had sex with an HIV-positive partner.

Recent Event Analysis

Table 4 shows the frequency of different drug-related activities occurring immediately before, during or immediately after recent events of partner violence. Of the thirty-one women who reported recent events, 83.9% percent (n=26) recalled events in which there was some drug-involvement; 40% (n=13) indicated that both they and their partners were involved in drug-related activities; 35% (n=11) reported that their partners had used drugs or alcohol or were trying to get money to procure drugs; and only two women (6.4%) indicated that they alone had used drugs or alcohol. One-fifth (19.3%) of the women (n=6) indicated that they had used drugs immediately after the event because they were upset or in physical pain. The use of drugs after an abusive event to calm down or to alleviate physical pain lends some credence to a trauma theory approach to explaining the violence drug use nexus.

Crack/cocaine was the most prevalent drug that the women reported using immediately before, during or immediately after the most recent violent event. One-fifth (19.3%) of the women indicated crack/cocaine use in conjunction with the most recent violent episode; in comparison, one-tenth reported heroin use and 6.4% reported alcohol use. For male partners, however, alcohol and crack/cocaine use were the most prevalent substances reported in conjunction with the most recent violent episode. Almost one-third of the women (29%) indicated that their partners were drinking immediately before or during the episode. One-quarter (25.8%) also reported that their partners had used crack/cocaine and 6.4% indicated that their partners were high or going through withdrawal from heroin.

In addition to the effects of drug and alcohol use, other drug-related factors were mentioned in conjunction with the most violent episode, although they were less prominent. Four women (12.9%) indicated that their partner's negative comments about their drug use triggered the conflict. This type of verbal abuse, which reinforces the low social status of drug-involved women, was mentioned frequently in the focus groups for this study (57) and has been noted in other qualitative studies (45, 58). Three women (9.6%) reported that an argument over their partners' asking for money or spending money on drugs set off or escalated the most recent violent event. This type of conflict suggests the presence of economic compulsive violence outlined in Goldstein's tripartite model (1985) (32). In addition, two women indicated that conflicts over procuring or splitting drugs set off or escalated the most recent violent event, which is typical of the systemic violence from drug use in Goldstein's model (1985) (32).

TABLE 4

Frequency of Drug-Related Activities and HIV Risk-Related Issues Immediately Before, During or Immediately After Most Recent Event of Partner Violence (n=31)

Drug-related activities before, during or after event	n	%
1. Any drug involvement by woman and/or partner	26	83.9
2. Drug involvement by woman and partner	13	41.9
3. Drug involvement by partner only	11	35.5
4. Drug involvement by woman only	2	6.4
Woman's drug use before, during or after event		
1. Woman's crack/cocaine use	6	19.3
2. Woman's heroin use	3	9.6
3. Woman's alcohol use	2	6.4
4. Any drug use by woman immediately after event	6	19.3
Partner's drug use before, during or after event		
1. Partner's crack/cocaine use	8	25.8
2. Partner's heroin use	2	6.4
3. Partner's alcohol use	9	29.0
Other drug-related involvement before or during event		
1. Arguments over partner spending money for drugs	3	9.6
2. Partner upset about woman's drug or alcohol use	4	12.9
3. Arguments over procuring or splitting drugs	2	6.4
Occurrence of HIV risk in conjunction with event		
1. Forced or unwanted, unprotected sex	6	19.3
2. Disclosure of an STD	0	—
3. Conflicts over condom use requests or refusals	0	—
4. Accusations of having outside affairs	9	29.0

In terms of HIV risk behavior, one-fifth of the women (n=6) reported that they had had unwanted sex during or after the most recent incident. None of these women reported using condoms during these incidents. None of the women reported that the recent incidents were triggered by disclosure of a sexually transmitted disease or conflict over using condoms. The lack of conflict over condom use may be related to the fact that few women reported that they had ever used condoms with their main partners. The occurrence of rape and low rate of ever using condoms with one's main partner may indicate that the need to protect oneself against HIV or HCV among this sample of abused women is overridden by the more pressing need to avoid violence.

The low rate of condom use among this group of women is of particular concern, given that two-thirds (67.7%, n=21) reported that they have had outside relationships or suspected that their partners have had outside relationships. In fact, almost one-third of the women (29%, n=9) reported that accusations of outside affairs triggered the most recent episode of abuse.

Case Studies

We selected three case studies which illustrate a range of the multiple ways in which drug-related activities and HIV risk-related issues insert themselves into episodes of partner violence. The case studies also provide the interpersonal and broader social context in which events occur.

Case 1

Elaine and Mike met in drug circles. They did crack and heroin, and both hustled to bring drugs for each other. During their relationship, Elaine's habit stayed pretty much the same, but Mike's habit got worse. As he became more addicted, he became more abusive. Elaine attributes much of his abuse to the drug use, although she admits that drug use also made her "mean" verbally.

The most recent event started over an argument as to whether Elaine should have an abortion. Elaine accused Mike of spending money on drugs rather than giving her money for an abortion. Mike claimed that he did not want her to end the pregnancy. They had an extended verbal argument. On the day of the fight, Elaine had done crack and heroin, and Mike had been smoking crack all day long. Elaine indicated that at the time of the fight she was not high, but she was physically exhausted and felt that the drug use had contributed to her feeling emotionally broken down. Mike, who was high on crack at the time, then started punching the walls and throwing things. When she tried to leave, he shoved her very forcefully away from the door and prevented her from exiting.

The fight ended when she threatened that she would never see him again if he did not let her go. Elaine indicated that Mike had turned violent because he had felt cornered by her accusations and that the crack had intensified those feelings. Immediately after the event, Elaine reported that she sniffed more heroin to calm down and had asked her friend to bring her some Valium.

In this particular event, drug use is integral to the context in which the abuse evolves and plays out, most directly in terms of the effect of crack use on Mike's violent response to Elaine's accusations and on Elaine's need to use heroin and Valium after the event. Elaine's state of exhaustion from drug use and the conflict over spending their money on Mike's drug use rather than the abortion also played a role in escalating the conflict into violence. Although HIV risk behavior was not directly linked to this event, their argument over whether or not to terminate Elaine's pregnancy demonstrates how HIV risk behavior may be related to wider conflicts over contraception and reproduction. This case illustrates the inherent difficulties of introducing condom use to couples like Elaine and Mike, where the male partner wants to have children and maintain control of reproduction decisions.

Case 2

Lenore and Ron have been together on and off for 20 years. They have four children together but are no longer living with each other. Ron introduced Lenore to heroin shortly after their first baby was born. He told her that heroin would increase her sex drive. Lenore believed that heroin did improve their sex life. She has been using heroin for the last ten years, although she has reduced her intake significantly since she entered methadone treatment two years ago. Lenore has never used condoms with Ron, even though she has had outside partners over the last three years. She claims that asking Ron to use a condom would make him think that she is having affairs, even though Ron has also had outside relationships while they have been together. Lenore is worried that if Ron ever found out about these affairs, he would kill her. She tested negative for HIV a couple of years ago, but he has never been tested.

During the most recent episode of violence, Lenore indicated that both she and Ron were high on heroin. They were lying in bed after having had vaginal sex, when Ron attempted to have anal sex. Lenore refused, but Ron yanked her ponytail and tried to penetrate by force. She then screamed and threatened to kill him, at which point he stopped. Lenore was so furious at Ron after this incident that she refused to have sex with him. One week later, when she was getting out of the shower, he threw her down on the bed and forced her to have vaginal intercourse.

For both Ron and Lenore, heroin has had strong sexual associations. In this event, expectancies about heroin use and sexual desire may have fueled Ron's attempt to force anal sex. Ron might have felt that his attempt to force anal sex while high on heroin would be forgiven. This explanation is consistent with the view that drug use is an instrument of domination and control used to excuse the exercise of violence against intimates (34, 35). Or alternatively, Ron might have misjudged cues, assuming that Lenore wouldn't object to having anal sex because she was high on heroin, which is more consistent with the psychopharmacological explanation that substance use induces cognitive disruption, which impairs the ability to process social interactions (33).

This event is laced with HIV implications. Unprotected anal sex is a particularly risky act. This event also involved a forceful attempt on Ron's part to restore sexual relations as a way of countering Lenore's refusal to have sex. The risk factors for HIV for Lenore and Ron are numerous. They have never used condoms with each other although both have had outside partners in the last three years, and both have had a long history of injecting drug use.

Case 3

The third case involves Rosa and her husband of 8 years, Juan. She had left Juan two months prior to the interview. Their relationship started to fall apart when Rosa stopped doing drugs. She lost her attraction for him and had less to say to him. She was more reluctant to give him any money. Juan suspected that her withdrawal of affection was a sign that she was seeing another man and became increasingly abusive. Rosa is HIV positive, and Juan has so far tested HIV negative. According to Rosa, Juan doesn't care if he gets the virus. He refuses to use male condoms — occasionally she has been able to use a female condom with him, but not consistently. Juan has had outside relationships, but Rosa has not.

The most recent event was triggered when Juan, who was drunk at the time, demanded money from Rosa for drugs. Rosa refused because she had planned to use the money to take her kids to the movies. Juan responded, "You ain't going nowhere, you f— bitch" and hit her hard in the face, causing her to crash into a steampipe. After the event she moved out to her mother's home, but after three days she was feeling lonely and, thinking that maybe she could work things out with Juan, she went back to the apartment. After talking to him and realizing that the relationship would not work, she started to pack her bags. When it became clear to Juan that she intended to leave him for good, Rosa said that he grabbed her by the hair, threw her down and started choking her. Rosa began to cry and told him that she wouldn't leave him. He stopped and told her he wanted to make love to her. She realized that she had no choice but to consent, although she said it made her feel dirty and hurt. They did not use condoms. Rosa then told him she had to go get her methadone. At this point she went with her kids to the battered women's shelter.

In this case, unprotected sex and drug involvement were integral to the way the abuse unfolded. For Rosa as well as Lenore, having sex after the event was critical to the cycle of contrition, a sign that the abuse was forgiven and normal relations resumed. Yet for these women, having unprotected sex after abuse was experienced as an unwanted but necessary act for avoiding further conflict. Clearly, in Rosa's case, refusing unprotected sex would have meant risking further life-threatening abuse.

For women like Rosa, the competing pressures of having to finance their partner's drug needs and to run a household inevitably forces them to make difficult decisions. Do they spend their dwindling dollars on their children or on preventing their partner from going through withdrawal? For some abused women in our sample, this kind of "economic compulsive" violence was chronic, with devastating repercussions of hunger, homelessness and loss of children to placement.

The success or failure of a woman's efforts to enter drug treatment or abstain from drugs will depend largely on the extent to which she has extricated herself from the influence of drug-using relationships. Yet this can be dangerous for women like Rosa, who are in abusive relationships. After she entered drug treatment, Juan's abuse escalated. Her attempt to leave drugs behind was perceived by Juan not only as a threat to the whole context of intimacy in their relationship but also as a threat to his access to drugs.

Discussion

By any measure, the prevalence of recent drug use, particularly crack/cocaine use and HIV risk behavior among this sample of abused women is disconcertingly high. The event analysis of recent episodes of partner violence in this study further suggests that drug-related activities played a significant role in contributing to and recovering from partner violence among this sample of women in MMTPs. Although no direct evidence implicated requests or refusals over condom use as a trigger for the most recent episode of partner violence, the underlying pervasive context of fear of partner violence may have preempted any negotiation of condom use. The multiple ways in which drugs inserted themselves into episodes of partner violence and the occurrence of coerced, unprotected sex during or after these episodes raises serious concerns about addressing relapse, and HIV and HCV prevention, among abused women in MMTPs.

The findings of this study suggest that the relationship between drug-related activities and partner violence is multi-faceted and complex. Consistent with the psychopharmacological explanations afforded by Goldstein's tripartite model (32), women in our sample attributed their experiences of abuse to their partner's drug use and to a lesser extent to their own drug use. For women, crack/cocaine use was most often implicated in partner violence episodes; whereas for male partners, alcohol and crack/cocaine use were the primary drugs cited in connection with partner violence episodes. Although a few women believed that their partners used drugs and alcohol as a way of excusing their violent behavior, most women believed that the pharmacological effects of drugs or alcohol unleashed their partner's violence or distorted their judgment or perception of situations, leading to violence.

Conflicts over spending money and procuring drugs were also cited as a trigger for partner violence episodes, consistent with economic compulsive explanation of violence (32). These conflicts often stemmed from an imbalance in gender role expectations, in which women were expected to provide drugs for their partners at the expense of their own needs and their children's needs. Many women in our sample felt that their partners demanded more from them and treated them worse because of their tarred reputation as drug-using women. Other researchers have also suggested that the low social status of drug-using women exacerbates the power imbalance in intimate relationships (20, 24, 48). Although only two women indicated conflicts over procuring or sharing drugs in the partner violence episodes reported in the in-depth interviews, many women in this study suggested that fights with their partner over how to divide drugs played a significant role in their victimization (57), consistent with a systemic explanation of violence (32).

Women were able to identify bi-directional connections between their drug use and their experiences of abuse. Most notably, several women indicated that they used drugs to alleviate the physical and emotional pain from the abuse, consistent with trauma theory. For women such as Elaine, the immediate use of drugs to calm down after an event may represent a "learned" response over years of coping with frequent stressful or traumatic situations. As long as drug use remains a primary coping mechanism in response to experiencing partner abuse, relapse is inevitable and termination of violence in the relationship is unlikely.

Women in this study are at very high risk of contracting HIV and HCV, for multiple reasons. Only a minority of our sample have ever used condoms with their partners although a majority reported that they or their partners have had outside relationships. Furthermore, one-fifth of the women injected drugs in the past year; another one-fifth of the women indicated that they had exchanged sex for money or drugs in the past 90 days, and almost one-fifth reported having had sex with an HIV-positive partner in the past 90 days.

Couples like the ones in the case studies present a serious challenge to HIV and HCV prevention efforts for many reasons. First, how do you introduce condom use in an abusive relationship, when condom use connotes outside affairs and any hint of other lovers is a powder keg for violence? Jealousy and suspicion of affairs played a significant role in triggering episodes of partner violence in this study. Even if a woman suspects infidelity, injection drug use, or other risk indicators, requesting that her partner use condoms or get tested for HIV may signal a lack of trust or caring on her part (59–61), may imply to her partner that she herself has engaged in other risky behaviors, and may threaten the stability of the partnership, increasing the likelihood of a violent outcome (62). Second, drug-involved poor women in power-imbalanced relationships, such as the women in our sample, perceive or face potential negative economic, social, and other acute consequences for denying sex to their partners or insisting on condom use (63–65). Third, given the wider constellation of pressing problems such as extreme poverty, homelessness, and loss of children to placement that many drug-involved women confront, their concern over HIV or HCV and their motivation to use condoms may rank low in priority (62). Moreover, for some women who subscribe to traditional gender roles, requesting or insisting that a man use a condom or get an HIV test runs against the grain of broader cultural norms which discourage women from talking about sex, initiating sexual practices, or otherwise controlling an intimate heterosexual encounter (64, 66–68). Weighing the benefit of using condoms against these potentially negative consequences (e.g., violence, loss of economic resources and compromised social status), it is not surprising that so few women in our sample had ever used condoms with their partners, despite their substantial risk of contracting HIV.

Health and social service personnel need to consider the multiple reasons why abused, drug-involved women do not use condoms. The standard skills taught to empower women to negotiate condom use with their partners is clearly contraindicated for abused women because of the potential violence they may encounter in response to suggesting condom use.

Because this study did not ask separate questions about risk behavior for HCV, we can only speculate how partner violence may be linked to HCV, based on the findings related to HIV risk. Clearly, this sample of women is at risk of HCV by virtue of their injecting drug use: one-fifth of the women report recent injection drug use, and the vast majority have injected drugs in the past. Further qualitative and quantitative research is needed to examine the relationship between partner violence and risk behavior, which is more specific to HCV. For example, are there types of violent sex or physical violence involving the exchange of blood which place women at risk of HCV? How does a woman's disclosure of HCV to her partner increase her risk of partner violence? Does the stress of living with HCV or living with an HCV-infected partner increase a woman's risk of partner violence? Do injecting-related practices (e.g., sharing needles, rinse water, cookers, cotton, backloading, and frontloading) vary in abusive and non-abusive intimate relationships? Given the host, environmental and viral factors which favor a rapid spread of HCV among IDUs (15), the need to explore these type of questions is especially paramount.

Implications for Treatment and Policy

Understanding how partner violence contributes to HIV and HCV risk and drug use is important if we are to develop policy, prevention and treatment strategies that will address more effectively the constellation of problems that abused, drug-involved women confront. Several prevention and treatment recommendations for abused women in MMTPs should be considered from the study findings, including:

1. **Instituting routine screening for partner violence during intake and annual physical exams** — If women are currently involved with abusive partners, counseling staff should at minimum be trained to develop a safety plan for women, and to provide referrals for ongoing treatment for problems related to domestic violence. Failure to address the basic need of safety for abused, drug-involved women may jeopardize their recovery. Women who are dealing with the dual problems of partner violence and substance abuse are unlikely to remain in drug treatment as long as the pull of their drug-dependent, abusive partner persists. It is also important for MMTP staff to understand that an abused woman's decision to enter treatment may increase the likelihood of violence if her partner perceives it as a threat to his access to drugs and the whole context of intimacy.

2. **Providing concrete services (e.g., housing, job training and placement, and securing benefits) and enhancing the social support network to increase financial and emotional independence of abused women from their partners** — Financial and/or emotional dependency on a partner may impede a woman from leaving an abusive situation, protecting herself from HIV and HCV, or refusing to engage in drug-related activities. In comparison to the chronic stress women experience from living in substandard conditions (e.g., hunger and homelessness), their concern about protecting themselves against HIV and HCV, relapse, or abuse may register low in priority.

3. **Addressing underlying trauma and related stress that many abused, drug-involved women present** — The use of drugs to numb the physical or emotional pain from a violent episode underscores the importance of developing alternative ways of coping with stressful situations and undoing the "learned response" of drug use. Furthermore, other research indicates that women who experience multiple traumas, including partner abuse, and exhibit the presence of post-traumatic stress disorder, are more likely to engage in HIV risk behavior (52–54).

4. **Raising awareness of the multiple ways in which drug-related activities increase risk of partner violence at an individual level as well as an interpersonal level and broader macro-level** — Using a cognitive behavioral skills building approach, women may learn to identify and

avoid drug-related triggers for partner violence as well as partner-violence-related triggers for drug relapse and HIV or HCV risk. By further increasing women's recognition of gender discrepancies in power and control over reproductive and drug-using practices, women can select more appropriate HIV and relapse-risk-reduction strategies, which may take into account their immediate need for safety, but which may ultimately redress the balance of power and control in their relationship. Finally, it is critical to raise awareness of these converging epidemics at a broader community level. Through targeted media and peer network approaches, women and men at risk may increase their awareness of the devastating impact of domestic violence, HIV, HCV and substance abuse on their community. Such heightened awareness may lead to increased participation in community activities and/or organizations that may further redress these problems by changing social norms and demanding increased prevention and treatment resources.

Conclusion

The findings of this study highlight the need for an integrated service system that can address the overlapping problems of partner abuse, HIV, HCV and addiction. MMTPs have played a pivotal role in reducing HIV risk behavior and drug use among IDUs (69). MMTPs may be an ideal setting to launch a contextually specific HIV, HCV and drug-relapse intervention program for abused, drug-involved women, given their substantial experience in HIV and relapse prevention, their frequent, ongoing contacts with patients, and the large number of abused women they serve. Clearly, such an intervention would require funding more support services than are currently available in most MMTPs. In addition to the social welfare benefits of providing such enhanced, integrated services, policy makers should consider the long-term economic costs of treating the disproportionately high number of cases of HIV infection, STDs, physical injuries, substance-abuse-related complications and other medical problems that abused, drug-involved women are likely to present.

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